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**COMORBIDITIES IN GOUT: STUDY OF CLINICAL POLYMORPHISM, DIAGNOSIS,
TREATMENT STRATEGIES AND PROGNOSIS**

321.04 – RHEUMATOLOGY

Summary of the thesis of doctor habilitate in medical sciences

CHIȘINĂU, 2024

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The doctoral thesis and the summary can be consulted at the National Library of the Republic of Moldova (31 August 1989 st. 78A, Chișinău MD-2012), at the Library of the *Nicolae Testemițanu* State University of Medicine and Pharmacy of the Republic of Moldova (165 Ștefan cel Mare și Sfânt bldv., Chisinau MD-2004), on the web page of the Institutional Repository of *Nicolae Testemițanu* State University of Medicine and Pharmacy (<https://repository.usmf.md/>) and on the web page of ANACEC (<https://www.cnaa.md/>).

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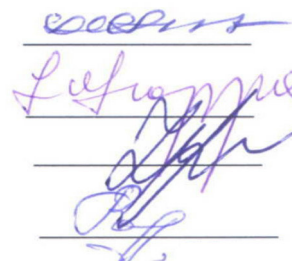
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CUPRINS

CONCEPTUAL MILESTONES OF RESEARCH.....	4
CONTENT OF THE THESIS.....	7
1. COMORBID ASPECTS IN GOUT.....	7
2. RESEARCH MATERIALS AND METHODS	8
3. FEATURES OF THE CLINICAL MANIFESTATIONS OF GOUT	10
3.1. Analysis of the comorbid background for gout in different age groups.....	10
3.2. Studying the incidence of dysmetabolic, cardiovascular, renal, osteoarticular diseases in investigated patients	14
4. COMORBIDITIES OF GOUT IN THE ELDERLY.....	19
4.1. Characteristics of elderly patients, provoking factors	19
4.2. Comparative analysis of comorbid diseases in elderly and adult patients	25
5. COSTS OF TREATING AN ELDERLY PATIENT WITH GOUT	30
5.1. Calculation and analysis of the direct costs of providing care to patients with gout by age and co- morbidity	30
5.2. Assessing the costs per case treated on an ongoing basis and developing principles to streamline expenditure in line with developments	31
GENERAL CONCLUSIONS.....	35
SUGGESTIONS FOR FUTURE RESEARCH	37
BIBLIOGRAPHIC REFERENCES.....	38
LIST OF SCIENTIFIC, SCIENTIFIC-METHODICAL, DIDACTIC WORKS.....	39
LIST OF ABBREVIATIONS	46
ADNOTARE.....	47
SUMMARY	48
PE3IOME.....	49

CONCEPTUAL MILESTONES OF RESEARCH

The actuality and importance of the studied topic. Gout is a disease characterized by the deposition of sodium monourate crystals in various tissues, organs and the onset of inflammation that develops as a result in patients with hyperuricemia (HU) caused by environmental and/or genetic factors [1-3]. The overall prevalence of gout varies between 1% and 4% and the incidence between 0.1% and 0.3%. The highest prevalence is found in Asia, driven by a genetic aspect. According to data from the Global Health Data Exchange (GHDx) registry [3] and the World Health Organization (WHO) database [4], in 2017 there were 7.44 million cases (incidence 0.097%) of gout worldwide, a prevalence of 4.22 million cases (0.54%) and 1.28 million deaths (0.051% of all deaths). In terms of gender distribution, over the last 25 years, men have been leading the incidence, prevalence and health loss related to gout. And this rate increases with age, up to 64 years, and correlates with the socio-demographic index (SDI). The risk of gout is three times higher in regions with a high SDI than in those with a low SDI. In 2005, 2.6 million new cases of gout were identified, with a prognosis of up to 3.6 million cases in 2025 [3]. WHO warns that the number of deaths from gout could increase by 55% in 2060 [4]. At the same time, in most developed countries of the world, the demographic situation is characterized by an increase in the relative number of elderly people, the frequency of occurrence of gout among them is highest, especially in those over 80 years of age, the prevalence reaches 11-13% and the incidence 0.4% [5]. The association of gout with cardiovascular and renal diseases, observed since the late 19th century [5], is now well established. The prevalence of comorbidities increases with the duration of gout [5], and gout is associated with all components of the metabolic syndrome [6]. Gout in elderly patients is characterized not only by a pronounced comorbid background, but also by a high risk of concomitant pathology, which causes difficulties in their management [6]. Gout requires additional economic costs both determined by the treatment of the disease itself and by concomitant pathogenetically associated pathological conditions [7]. However, despite the recent increased interest in the problem of gout in the elderly, the number of studies aimed at a comparative analysis of the disease in different age groups is limited and confined to the description of individual clinical cases [8]. An unresolved question remains - what contributes to the progression of gout in the elderly, the characteristics of its onset in these patients not being clearly determined. Also, in recent studies, the clinical and economic aspect of gout has not been elucidated.

Aim of the study. To assess the comorbidity of patients of different ages affected by gout with clinical and economic rationale for improving the management of clinical-paraclinical assessment in providing care to these patients.

Study objectives. 1. Assessment of comorbid status in gout patients of different ages. 2. Analysis of the evolution of the inflammatory process and disease progression in patients with gout in the different decades of age. 3. Specify the pathological changes of internal organ pathology and the evolutionary peculiarities of extra-articular damage in patients with gout. 4. Determine the triggering factors and their influence on the onset, characteristics and evolution of gout in the elderly. 5. Analysis of the possibility of correcting modifiable risk factors in elderly patients by adjusting non-pharmacological and

pharmacological treatment. 6. Determination of economic feasibility expressed by analysis of direct medical costs according to age and comorbidity, with elaboration of principles of cost efficiency.

7. Economic cost analysis of an inpatient case, with development of cost efficiency principles according to evolution. 8. Development of recommendations for streamlining clinical management and economic feasibility of providing care to elderly patients with gout.

The scientific novelty of the study. Challenging factors, onset and progression, frequency of comorbidities in elderly patients with gout compared to similar indicators in patients of other age groups were assessed. An assessment of the compliance of the „typical practice” management of elderly patients with gout in a hospital setting was performed, taking into account the international guidelines valid for the study period. The importance of acquired controllable factors affecting the severity of gout in elderly patients was demonstrated, including: the administration of diuretics and low doses of Acetylsalicylic acid, obesity, dietary compliance and excessive alcohol consumption. Recommendations for improving the methodology of clinical and economic cost analysis of healthcare delivery for elderly patients with gout, taking into account the correction of the comorbid context, have been reviewed and are scientifically substantiated and tested.

The theoretical significance and application value of the work. The epidemiological data obtained on the frequency distribution of gout-causing factors in elderly patients allow risk stratification in these patients that we used in creating recommendations for prevention and treatment of the disease. The characteristics of the onset and progression of gout in elderly patients that were identified during the study, compared to middle-aged patients, optimized the deployment of diagnostic and therapeutic measures in patients of this age group. Based on the analysis of factors causing gout in the elderly, the main methods of optimal approach to its prevention and treatment were identified, which include drugs (diuretics, Acetylsalicylic acid), dietary non-compliance, alcohol consumption and the presence of metabolic syndrome. Based on the data obtained, the significant role of comorbidities in shaping the costs of providing care to elderly patients with gout was determined. In particular, the presence of ischemic heart disease, chronic heart failure, chronic kidney disease significantly increases these costs. Methodological recommendations are presented for optimizing the methodology for modeling the costs of providing health care to an elderly patient with gout, taking into account comorbidities, which include reviewing the number of examinations, both laboratory and instrumental, for each comorbid disease.

Implementation of results. The results of the study have been included in the didactic activity of the Internal Medicine Department of the *Nicolae Testemitanu* State University of Medicine and Pharmacy, they are applied in the practice of the Arthrology Department of the *Timofei Moşneaga* Republican Clinical Hospital. Research results were reported at 21 national and international forums: **at international congresses:** III Евразийский Конгресс Ревматологов, Беларусь, Минск, 26 Мая, 2016; XXIII National Congress of Rheumatology. Romania, Bucharest, 13 October, 2016; 29th National Congress of Rheumatology in France. France, Paris, 12 December, 2016; VII Съезд Ревматологов России. Российская Федерация, Москва, 28 Апреля, 2017; XXV National Congress of Rheumatology.

Romania, Poiana Brasov, 11-13 October, 2018; International Congress of „Apollonia” University of Iasi, „Preparing the future by promoting excellence”, Romania, Iasi, 28 February, 2019; Всероссийский Конгресс с Международным Участием „Дни Ревматологии в Санкт-Петербурге 2019”, Российская Федерация, Санкт-Петербург, 23-24 Сентября, 2019; XXVI National Congress of Rheumatology. Romania, Poiana Brasov, 5 October, 2019; International Congress of the University „Apollonia” of Iasi. "Preparing the future by promoting excellence", Romania, Iași, 28 February, 2020; V Евразийский Конгресс Ревматологов с международным участием в формате онлайн, Российская Федерация, Москва, 24-26 Сентября, 2020; International Congress of the University „Apollonia” of Iasi in online format. „Preparing the future by promoting excellence”, Romania, Iași, 02 March, 2021; International Congress of the University „Apollonia” of Iași in online format. „Preparing the future by promoting excellence”, Romania, Iasi, 01 March, 2022; International Congress of „Apollonia” University of Iasi. „Preparing the future by promoting excellence”, Romania, Iasi, 03 March, 2023; European Exhibition of Creativity and Innovation, 15th edition of Euroinvent - 2023, Romania, Iasi, 12 May, 2023; World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, Spain, Barcelona, May 4-7, 2023; National Congress of Rheumatology. Romania, Cluj-Napoca, 7 October, 2023; **At national congresses:** „Gout - at the border between specialties”. Republic of Moldova, Chisinau, 29 March, 2018; 8th Congress of Urology, Dialysis and Renal Transplantation of the Republic of Moldova with international participation, Republic of Moldova, Chisinau, 7 June, 2023. International Innovation and Technology Transfer Exhibition „Excellent Idea – 2023”, 2nd edition, Republic of Moldova, Chisinau, 21 September, 2023; Annual Scientific Conference „Research in Biomedicine and Health: Quality, Excellence and Performance”, Republic of Moldova, Chisinau, 19 October, 2023; International Specialized Exhibition INFOINVENT 2023, Chisinau, 22-24 November, 2023.

The thesis was discussed, approved and recommended for defense at the meeting of the Discipline of Rheumatology and Nephrology, Department of Internal Medicine, *Nicolae Testemitanu* State University of Medicine and Pharmacy (Minutes no.4 of 20.09.2023), at the meeting of the Scientific Seminar of Profile: Profile: 321 – General Medicine/Specialty 321.01 – Internal Diseases (Nephrology), 321.04 – Rheumatology, 313.01 – Immunology (Minutes no.9 of 30.10.2023); at the meeting of the Senate of the *Nicolae Testemitanu* State University of Medicine and Pharmacy (Minutes no.13/18 of 21.12.2024).

Publications on the thesis topic. The study materials were reflected in 62 scientific publications, including 6 articles in peer-reviewed journals, 2 authored publications, 21 presentations and abstract communications at conferences, congresses, scientific exhibitions: 5 national and 16 international.

Keywords. uric acid, hyperuricemia, gout, metabolic diseases, comorbidities, diagnosis, severity score, economic costs.

Summary of thesis compartments. The paper is laid out on electronic text pages and is divided into: introduction, 5 chapters, discussion, 8 conclusions and 12 practical recommendations. The bibliographic index cites 240 literary sources. The thesis is illustrated with 45 tables, 36 figures. In Chapter 1, a synthesis of the data presented in the literature on gout was made, tracing the history of

research development, clinical expression, disease classification criteria, as well as modern assessment tools of specific impairment in patients with gout. Emphasis was placed on recent evidence on the management of patients with gout according to patient age (separated for patients under 60 and over 60), including social support, social-economic status of the patient with gout, and methods of cost estimation were demonstrated. In Chapter 2, the study design, methods of research and investigation of patients, criteria for inclusion and exclusion from the research, general characteristics of patients included in the study and methods of statistical analysis applied were described. The collected data were processed using IBM SPSS Statistics 26 and R-studio programs. In Chapter 3, the results gathered from the observational, descriptive, cross-sectional research on a group of 501 gout patients were analysed and described in figures and tables. The following were assessed, with cynical assessment tools: clinical-paraclinical characteristics of patients with gout according to their activity, exacerbations and age, degree of severity – chronicity, therapeutic regimens and hypouricemia. In Chapter 4, the results of the descriptive, selective study to estimate anthropometric and socio-economic status in patients with gout according to disease onset, age and paraclinical data - all attributed to the difference in expression according to patient age – were presented. Differences between groups were discussed in terms of clinical manifestations, objective and laboratory status, and the impact of gout and comorbidities on the patient. In Chapter 5, cost assessment of a large sample of clinical protocols used in the treatment of patients with gout was presented, taking into account not only the main disease but also comorbidities. Special attention was paid to elderly people. The technical functions of the TCAT were described in detail, illustrating the efficiency of this costing tool. The hospitalisation rate during the year was used for the calculations. The costs of treating gout and each of its accompanying diseases for 1 calendar year were determined. The annual cost of outpatient treatment of each disease was estimated according to the NCP, which is the same amount in groups [8]. The Discussion section focuses on the analysis of the topic in comparison with data from the literature.

General conclusions and practical recommendations summarise the theoretical conclusions and practical recommendations resulting from the findings and the scientifically substantiated arguments mentioned in the research.

CONTENT OF THE THESIS

1. COMORBID ASPECTS IN GOUT

The first chapter is dedicated to the literature review of the last 5 years on the topic of the thesis, with a thorough approach to various aspects, including: prevalence, incidence, provoking factors, including diet, alcohol consumption, overweight and metabolic syndrome in the development of gout, medication administration, influence of hypertension, presence of chronic kidney disease (CKD), association with other rheumatological diseases – osteoarthritis, psoriatic arthritis at different ages of patients with gout. The literature data analysis was performed in terms of hyperuricemia approaches, relationships of hyperuricemia and gout with morbidity and mortality in these patients, joint impairment and references to comorbidities (dyslipidemia, obesity, insulin resistance (IR), type 2 diabetes mellitus

(T2DM), hypertension, ischemic heart disease, chronic heart failure (CHF), CKD) depending on the age of patients. Also, the literature summary on the quality of healthcare and the clinical-economic analysis in determining the costs of treatment for elderly patients with gout were carried out.

2. RESEARCH MATERIALS AND METHODS

The study was conducted in accordance with the scientific postdoctoral program at the Department of Rheumatology and Nephrology of the *Nicolae Testemitanu* State University of Medicine and Pharmacy. This study was carried out with the financial support of the National Agency for Research and Development, in the framework of the „Postdoctoral Programs”, project „Comorbidities in gout: study of clinical polymorphism, diagnosis, treatment strategies and prognosis” with the number 22.00208.807.02/PDI. In order to achieve the proposed aim and objectives, the current research examined patients with gout according to the diagnostic criteria according to EULAR/ACR 2015, consecutively hospitalized in the period 2017-2022, in the departments of Rheumatology, Arthrology and Nephrology of *Timofei Moşneaga* Republican Clinical Hospital. The study was conducted in five phases.

Stage I. Description and planning of the research project with definition of the purpose, scientific research objectives and research hypothesis. At this stage, the scientific literature in the field was studied with the identification of the unexplored aspects, the research problem was outlined and the work plan formulated, the research objectives were set, the phenomena and processes subject to observation and analysis were identified, and the research hypothesis was formulated. This was followed by the selection of research methods and the development of the research design, planning and organization of the research, carrying out preparatory activities for the collection of primary material (selection and study of statistical databases, identification and development of questionnaires, approval of the research protocol within the Research Ethics Committee of the *Nicolae Testemitanu* State University of Medicine and Pharmacy (minutes no.13 of 20.09.2019). At this stage it was possible to identify the data collection issues for our study. If, initially, this study was to have a prospective character, then, due to the COVID-19 (SARS-CoV-2) pandemic, which invaded our country (from 11.03.2020, but it was not clear when it will be completed, according to the WHO forecast it was predicted until 2024, i.e. during the period of the planned research), active patient access was prohibited, contacts and patient movements from home to hospital were minimized – the study was changed to a mostly descriptive, cross-sectional one and the number of patients was increased from 300 to 501, which was not reflected on the final results.

Stage II. Collection of primary material and statistical processing of data. All patients with gout (diagnosis was established according to EULAR/ACR 2015 criteria) in the Nephrology, Rheumatology and Arthrology wards of *Timofei Moşneaga* Republican Clinical Hospital during 2017-2022 were analyzed according to established comorbidities. According to the inclusion and exclusion criteria, 501 patients (women – 78 patients, men – 423 patients) were included in the observational, descriptive, cross-sectional study. Patients were divided into two groups: group I – patients <60 years (n=233), group II – patients ≥60 years (n=268). Data collection was carried out with the help of the internal information system of *Timofei Moşneaga* Republican Clinical Hospital – „HIPOCRATE” (Protocol: Hyper Text Transfer Protocol with

Privacy). *Criteria for inclusion of patients* in the study were: 1. age for patients of both sexes over 18 years; 2. established diagnosis of gout according to EULAR/ACR 2015 criteria; 3. presence of informed consent. *Criteria for exclusion of patients* in the study were: 1. oncological pathology; 2. lack of informed consent. Comorbid pathology was diagnosed according to the National Clinical Protocols (<https://ms.gov.md/legislatie/ghiduri-protocoale-standarde>). A special unified form was developed for data collection. When reviewing the medical documentation, data from the anamnesis (alcohol use, dietary characteristics, medications (diuretics and Acetylsalicylic acid), drug treatment of gout, number of anamnestic gouty attacks, number of joints affected during the disease were recorded, presence of tophi, comorbid diseases associated with gout (hypertension, ischaemic heart disease, chronic heart failure, chronic kidney disease, type 2 diabetes mellitus), anthropometric indicators (height, body weight), presence and characteristics of arthritis were noted.

Stage III. *Statistical processing of the data obtained STATISTICA 26.0 (StatSoft, USA).* The collected data were processed using IBM SPSS Statistics 26 and R-studio programs. For continuous (quantitative) variables, mean value with standard deviation, median with interquartile range, minimum and maximum value were estimated and the data were visualized using histograms, Q-Q Plot, boxplot and heatmap.

Stage IV. *Interpretation of the statistical results obtained.* The results obtained enabled us to:

1. Calculate and analyse the direct costs of providing care to patients with gout according to age and comorbidity.
2. Develop recommendations for improving the methodology of clinical and economic analysis of the costs of providing health care to elderly patients with gout.
3. We assess the costs per stationary treated case and develop principles for streamlining expenditure according to developments.

Stage V. *Drawing up conclusions and practical recommendations, practical implementation of research results.* Conclusions and practical recommendations have been formulated. The obtained results were proposed for practical implementation in *Timofei Moşneaga* Republican Clinical Hospital, Departments of Rheumatology, Arthrology and Nephrology, on the basis of which innovations were developed (5 Certificates of Innovator and 5 Acts of Implementation of Innovation): the diagnosis of gout was performed according to the classification criteria for gout according to ACR/EULAR 2015. Objective, laboratory and instrumental patient examination was performed according to the National Clinical Protocols „Gout in adults”. Determination of the cost of treating the disease is done by clinical and economic analyses, whose task is to calculate the „cost of disease”. We presented an observational, descriptive, cross-sectional study using clinical-paraclinical and treatment data of patients in the Departments of Rheumatology, Arthrology and Nephrology wards of *Timofei Moşneaga* Republican Clinical Hospital, in which the planned objectives were solved, solved by elaboration/comparative evaluation of gout in young and elderly patients, the net result being the identification of usual/alternative predictive models for comorbidities and solitary developments.

3. FEATURES OF THE CLINICAL MANIFESTATIONS OF GOUT

3.1. Analysis of the comorbid background for gout in different age groups

501 patients with gout, mean age 60.2 ± 8.3 years [56; 65]. Were selected of which 78 (15.6%) (95% CI, 12.6%-18.9%) were women and 423 (84.4%) (95% CI, 81.1%-87.4%) were men. The age of patients tended towards 63 years (median, interquartile deviation 12) in females and 60 (median, interquartile deviation 7) in males (Figure 3.1). Patient age trended towards 63 (median, interquartile range (IQR) 12) in women and 60 (median, interquartile range (IQR) 7) in men (Figure 3.1).

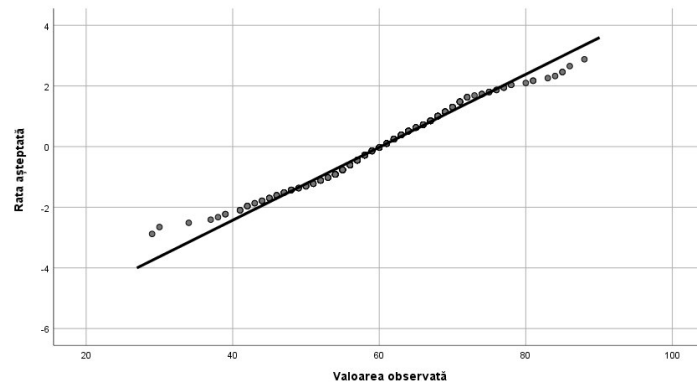


Fig. 3.1. Age-based distribution analysis

The median age of onset in 501 gout patients (423 men and 78 women) was 49.2 [36.9; 59.9] years. The age of gout onset among male and female study participants did not differ significantly (48.1 ± 12.9 years and 50.3 ± 14.3 years, respectively, $p=0.3$). Mean disease duration was 11.2 [8.02; 16.3] years.

Distribution of patients by age, sex and severity of gout: women – mild 49 ± 7.0 [30; 58] (95% CI, 46%-55%), medium 65 ± 7.0 [41; 88] (95% CI, 60%-67%), severe 57 ± 8.0 [52; 67] (95% CI, 52%-67%); men – mild 52 ± 6.0 [29; 68] (95% CI, 48%-55%), medium 62 ± 7.0 [34; 85] (95% CI, 58%-66%), severe 63 ± 10.0 [42; 86] (95% CI, 56%-70%). According to the distribution of the patients included in the study according to the degree of severity of the disease (data summarized in Figure 3.2), we find the predominance of forms of gout with medium and severe degrees of severity, dependent on advancing age. The interdependence of clinical form, age and comorbidities (senile included) plays an important role in the expression of clinical manifestations in elderly patients.

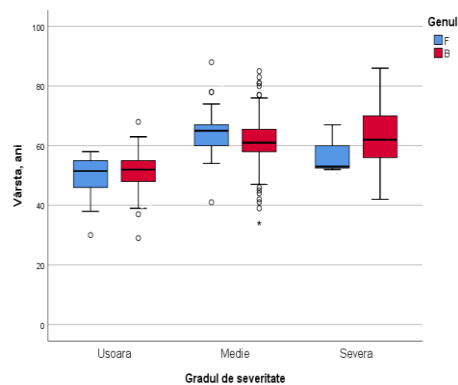


Fig. 3.2. Distribution of study patients by severity by gender

The relationship between severity and gender on the one hand and age on the other was subjected to factorial analysis of variance. The results presented in Table 3.1 show a significant overall effect ($F=38.906$), ($\chi^2=0.282$, $p=0.001$), which comes entirely from the main effect of the factor – sex ($F=71.028$), ($\chi^2=0.223$, $p<0.001$) and of the factor – degree of severity ($F=10.0$), ($\chi^2=0.016$, $p=0.001$). Thus, the degree of severity/sex interaction shows an association with age of gout patients.

Table 3.1. Multiple comparisons by patient age and severity

Degree of severity	Comparison between degrees of severity	Average difference	Standard error	p	95% CI,	
					lower limit	upper limit
Mild	Medium	-11.01*	0.826	0.000	-12.96	-9.07
	Severe	-11.15*	1.172	0.000	-13.90	-8.39
Medium	Mild	11.01*	0.826	0.000	9.07	12.96
	Severe	-0.13	0.990	0.990	-2.46	2.19
Severe	Mild	11.15*	1.172	0.000	8.39	13.90
	Medium	0.13	0.990	0.990	-2.19	2.46

Note: CI – confidence interval; $p=0.005$.

Multiple comparisons performed by Tukey post-hoc procedure (Bonferroni corrections) showed statistical significance (Table 3.1) for the comparative age assessment between the medium severity and severe severity groups compared to mild severity ($p<0.001$), absolute difference 11.01 medium severity (95% CI, 9.07%-12.96%) ($p<0.001$), absolute difference severe severity 11.15 (95% CI, 8.39%-13.9%), respectively.

The age value in patients with medium severity and severe severity is without statistical significance ($p=0.990$), absolute difference 0.13 (95% CI, 2.46%-2.19%) and these data were confirmed by homogeneity analysis of the groups investigated (Table 3.2), which allows us to affirm the high veracity of the results obtained.

Table 3.2. Analysis of homogeneity in the investigated groups

Degree of severity	n=501	Subset	
		Age patients <60	Age patients ≥60
Mild	93	51.20	
Medium	348		62.22
Severe	60		62.35
p		1.000	0.991

Note: n – number of patients (absolutely).

The number of affected joints depends on the severity of gout: mild 1 ± 1.0 [1; 4], medium 8 ± 4.0 [3; 19], severe 15 ± 2.0 [10; 20] with statistically significant difference also by gender – for women – mean number of affected joints 7 ± 5.0 [1; 18] and for men – mean number of joints 8 ± 3.0 [1; 20], without statistically significant difference.

Presence of tophi according to severity: mild grade – absence of tophi; medium grade – 81 (23.3%) (95% CI, 19.1%-27.9%) patients, severe grade – tophi are identified in all patients; by sex: female – 12 (15.4%) (95% CI, 26.3%-35.0%). According to the data presented, we can conclude that as the clinical form of gout progresses in severity, the incidence of tophi increases, being in high numbers in severe forms. This is consistent with the literature data, which confirms a close pathogenetic link between gout, chronic hyperuricemia, patient age and comorbid pathologies, particularly renal.

The mean duration of stationary treatment of mild and medium grade gout was 7±1.0 [5; 8] days; severe – 9±1.0 [7; 10] days. Of course, it is obvious that with increasing severity of gout, which predicts a complicated clinical course, involvement and functional decompensation of many organs and systems, with accentuation of comorbid diseases – increases the duration of inpatient treatment, which is statistically significantly longer, compared to mild forms, predicts massive involvement and expenditure of the health budget.

Table 3.3. Distribution of nosological units from the category of concomitant pathologies to the examined group of patients with gout

Nosology	n=501	%	95% CI, lower limit	95% CI, upper limit
Hypertension	412	82.2	78.7	85.4
Osteoarthritis	412	82.2	78.7	85.4
Chronic pancreatitis	402	80.2	76.6	83.5
Ischemic heart disease	390	77.8	74.1	81.3
Degenerative spondyloarthritis	388	77.4	73.6	80.9
Chronic tubulointerstitial nephropathy	316	63.1	58.8	67.2
Dyslipidemia	236	47.1	42.8	51.5
Nephrolithiasis	196	39.1	34.9	43.4
Hepatic steatosis	129	25.7	22.1	29.7
Obesity	126	25.1	21.5	29.1
Type 2 diabetes mellitus	90	18	14.8	21.5
Psoriatic arthritis	49	9.8	7.4	12.6

Note: CI – confidence interval; n – number of patients (absolute); % – the number of patients in percent.

In terms of the distribution of comorbidities, 5 pathologies predominated in the study group, among which hypertension in 412 patients (82.2%) (95% CI, 78.7%-85.4%), OA in 412 patients (82.2%) (95% CI, 78.7%-85.4%), chronic pancreatitis in 402 patients (80.2%) (95% CI, 76.6%-83.5%), ischaemic heart disease in 390 patients (77.8%) (95% CI, 74.1%-81.3%) and degenerative spondyloarthritis in 388 patients (77.4%) (95% CI, 73.6%-80.9%). Kidney damage in the patients investigated was manifested by the presence of chronic tubulointerstitial nephropathy in 316 patients (63.1%) (95% CI, 58.8%-67.2%) and/or nephrolithiasis in 196 patients (39.1%) (95% CI, 34.9%-43.4%). The presence of dyslipidaemia is identified in 236 patients (47.1%) (95% CI, 42.8%-51.5%); other aspects of these disorders are the presence of obesity in 126 patients (25.1%) (95% CI, 21.5%-29.1%) and hepatic steatosis (with USG signs) in 129 patients (25.7%) (95% CI, 22.1%-29.7%), the presence of type 2 diabetes mellitus in 90 patients (18%) (95% CI, 14.8%-21.5%). In our study, in 49 patients (9.8%) (95% CI, 7.4%-12.6%), in addition to gout, psoriatic arthritis was present (Table 3.3).

After the distribution of the nosological units in the category of comorbidities in the group of patients with gout examined, according to sex, the statistically significant difference is observed according to two pathologies: obesity more frequent in women – 31 (39.7%) (95% CI, 29.4%-50.8%) than in men – 95 (22.5%) (95% CI, 18.7%-26.6%) ($\chi^2=10.452$, $df=1$, $p=0.001$), but nephrolithiasis more often present in men – 174 (41.1%) (95% CI, 36.5%-45.9%) and in women – 22 (28.2%) (95% CI,

19.1%-38.8%) ($\chi^2=4.623$, $df=1$, $p=0.032$). It is important to mention, that sometimes the presence of nephrolithiasis in men is a primary sign within purine disorders. Other nosological units investigated do not show a statistically significant difference according to sex, being distributed as follows: chronic pancreatitis – 67 (85.9%) of women (95% CI, 76.9%- 92.3%) and 335 (79.2%) of men (95% CI, 75.15%-82.9%) ($\chi^2=1.865$, $df=1$, $p=0.172$), hypertension – 62 (79.5%) of women (95% CI, 69.6%-87.3%) and 350 (82.7%) of men (95% CI, 78.9%-86.1%) ($\chi^2=0.478$, $df=1$, $p=0.489$), osteoarthritis – 63 (80.8%) of women (95% CI, 71.0%-88.3%) and 349 (82.5%) of men (95% CI, 78.7%-85.9%) ($\chi^2=0.136$, $df=1$, $p=0.712$), degenerative spondyloarthritis – 62 (79.5%) women (95% CI, 69.6%-87.3%) and 326 (77.1%) men (95% CI, 72.9%-80.9%) ($\chi^2=0.221$, $df=1$, $p=0.639$), ischemic heart disease – 58 women (74.4%) (95% CI, 63.9%-83.0%) and 332 men (78.5%) (95% CI, 74.4%-82.2%) ($\chi^2=0.651$, $df=1$, $p=0.420$), chronic tubulointerstitial nephropathy – 56 women (71.8%) (95% CI, 61.2%-80.9%) and 260 men (61.5%) (95% CI, 56.8%-66.0%) ($\chi^2=3.017$, $df=1$, $p=0.082$), dyslipidaemia – 36 women (46.2%) (95% CI, 35.4%-57.2%) and 200 men (47.2%) (95% CI, 42.6%-52.0%) ($\chi^2=0.034$, $df=1$, $p=0.855$), hepatic steatosis – 24 women (30.8%) (95% CI, 21.4%-41.6%) and 105 men (24.8%) (95% CI, 20.9%-29.1%) ($\chi^2=1.218$, $df=1$, $p=0.270$), type 2 diabetes mellitus – 20 women (25.6%) (95% CI, 17.0%-36.1%) and 70 men (16.5%) (95% CI, 13.2%-20.3%) ($\chi^2=3.695$, $df=1$, $p=0.055$). We revealed the presence of type 2 DM in 42.1% and a carbohydrate metabolism violation in 57.4% of cases. Such a high incidence of type 2 diabetes mellitus and its antecedent conditions (impaired glucose tolerance) should underlie aggressive correction of the causative factors of this disease and its timely diagnosis. In addition, the presence of type 2 DM increases the risk of developing atherosclerosis-related cardiovascular disease. After distributing the nosological units in the category of comorbidities in the group of gout patients examined according to sex, the statistically significant difference is observed after two pathologies: obesity which is present in women 31 (39.7%) (95% CI, 29.4%-50.8%) more frequently than in men 95 (22.5%) (95% CI, 18.7%-26.6%) ($\chi^2=10.452$, $df=1$, $p=0.001$), but the presence of nephrolithiasis more often attested in men – 41.1%, and in women – 28.2% ($\chi^2=4.623$, $df=1$, $p=0.032$).

The distribution of comorbidities according to lesion severity, represented in 3 grades (mild, medium, severe), revealed the relatively higher frequency ($\chi^2=11.690$, $df=2$, $p=0.003$) of chronic tubulointerstitial nephropathy in 48 (80.0%) of patients with severe grade (95% CI, 68.6%-88.6%) compared to those with mild grade – 49 (52.7%) of patients (95% CI, 42.6%-62.6%) of patients or medium – 219 (62.9%) of patients (95% CI, 57.8%-67.9%). Relatively higher frequency of nephrolithiasis for medium grade – 111 (31.9%) of patients (95% CI, 27.2%-36.9%), compared to mild grade – 29 (31.2%) of patients (95% CI, 22.5%-41.1%) or severe grade – 56 (93.3%) of patients (95% CI, 84.9%-97.7%). Dyslipidemia is more common in medium grade – 138 (39.7%) of patients (95% CI, 34.6%-44.9%), followed by severe degree – 56 (93.3%) of patients (95% CI, 84.9%-97.7%) and mild degree – 42 (45.2%) of patients (95% CI, 35.3%-55.3%). Osteoarthritis was more often detected at medium degree of severity – 284 (81.6%) of patients (95% CI, 77.3%-85.4%), mild degree is accompanied by osteoarthritis – in 68 (73.1%) of patients (95% CI, 63.5%-81.3%), and the severe degree

– only in 60 (11.9%) of patients (95% CI, 8.4%-23.9%). The other pathologies: type 2 DM, chronic pancreatitis, obesity, hepatic steatosis, hypertension, ischemic heart disease, psoriatic arthritis, degenerative spondylopathy – did not show a statistically significant difference by severity degree.

Observation of our patients showed that gout, independent of other provoking factors, increased the likelihood of myocardial infarction by 24.6%, which we explain by the influence of HU. Similarly, we observed that when using a multivariate model, adjustment for age, hypertension, dyslipidemia, impaired kidney functional capacity, type 2 DM, alcohol consumption, smoking, and body mass index (BMI) is taken into account. Thus, it was found that the risk of developing CHF and left ventricular systolic dysfunction was increased when gout was combined with heart failure, and when gout was combined with heart failure, an increase in patient mortality was observed, and by this we can explain the lower rate of patients with severe than those with medium severity of gout.

3.2. Studying the incidence of dysmetabolic, cardiovascular, renal, osteoarticular diseases in investigated patients

Dysmetabolic diseases. The main components of MS currently include abdominal obesity, impaired lipid and carbohydrate metabolism, hypertension and insulin resistance. Our study showed that the frequency of MS in patients with gout in different age groups is 1.6-2.8 times higher than in the population, reaching 65% in patients over 60 years of age. The frequency of detection of individual components of MS in patients with gout is also quite high and made it possible to diagnose MS in 68% of cases, insulin resistance – in 67% of cases, type 2 DM – in 18% of cases, among which medium severity predominated (Figure 3.3).

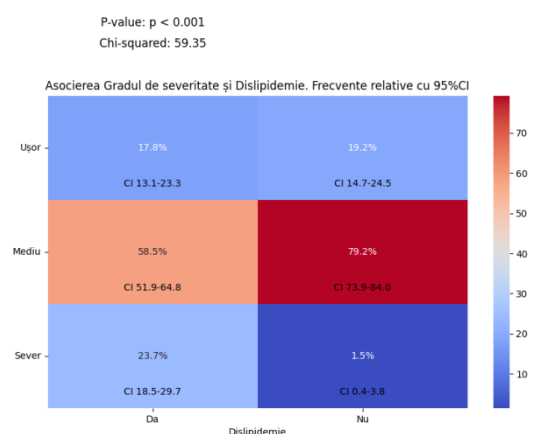
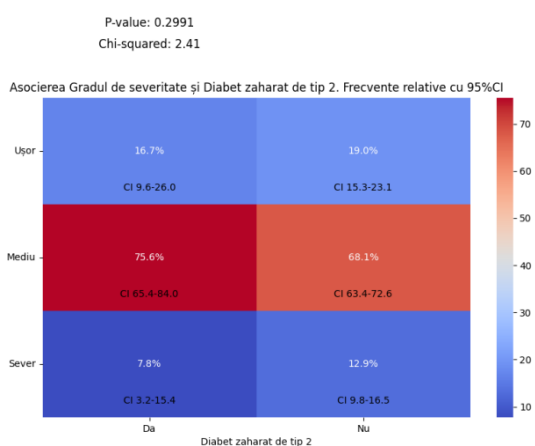


Fig. 3.3. Distribution of the severity of type 2 diabetes among the patients included in the study

Fig. 3.4. Distribution of dyslipidemia severity among patients included in the study

According to our data, the youngest patients with gout (up to 40 years of age) had the highest degree of dyslipidemia (Figure 3.4) and obesity (Figure 3.5) severity detected, causing, despite the increase with age in the frequency of hypertension and type 2 DM, the absence of age differences in the frequency of MS and insulin resistance detection.

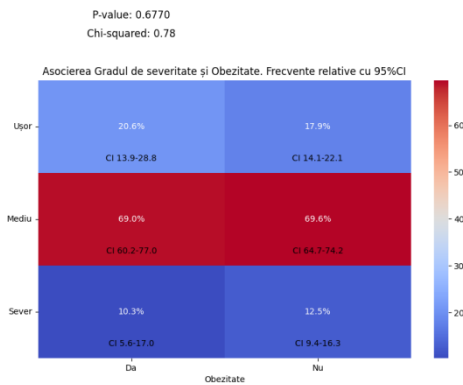


Fig. 3.5. Distribution of obesity severity among the patients included in the study

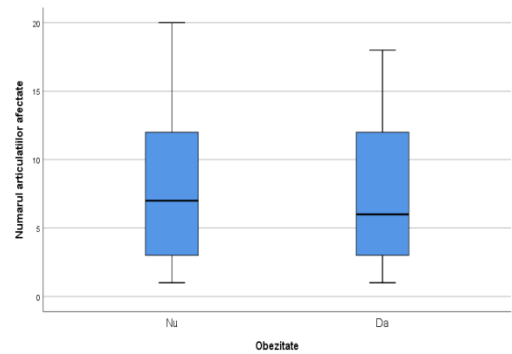


Fig. Mean number of joints affected in gout and severity of obesity in patients included in the study

The correlation of the mean number of affected joints with the degree of severity of obesity showed a strict and significant interdependence between these values. Thus, obesity played an important role as a causative factor for an adverse development of gout with a tendency towards polyarticular expression (Figure 3.6).

Cardiovascular diseases. Another disease that affects the development of gout is hypertension. According to the results of our study, hypertension was detected in 82.2% of patients with gout. We compared, by sex and severity, the presence of hypertension and ischaemic heart disease (Figures 3.7 and 3.8).

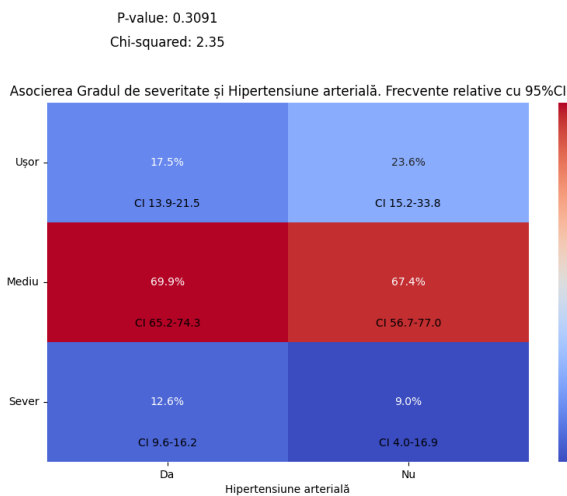


Fig. 3.7 Distribution of the severity of hypertension in the patients included in the study

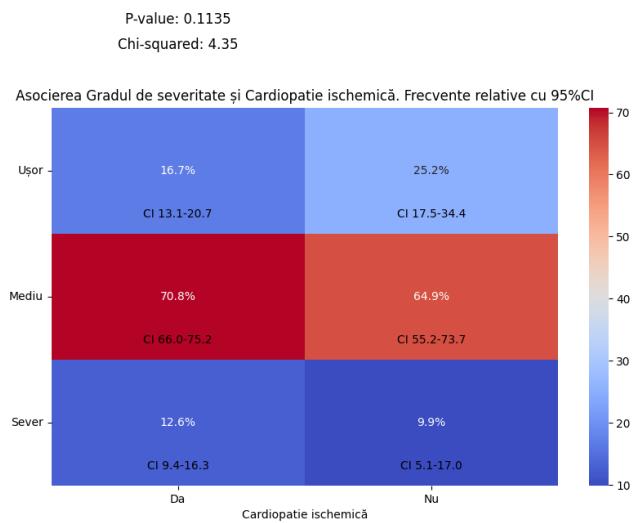


Fig. 3.8 Distribution of the severity of ischemic heart disease in the patients included in the study

In women, medium grade hypertension is predominant – 45 (78.9%) patients (95% CI, 67.1%-87.9%), followed by mild grade hypertension – 14 (77.8%) patients (95% CI, 55.4%-92.0%), severe grade hypertension is present in all patients – 3 (100%) cases. In men the most common cases are of medium grade of hypertension – in 243 (83.5%) patients (95% CI, 78.9%-87.4%), as in women, followed by severe grade – 49 (86.0%) patients (95% CI, 75.3%-93.1%) and mild grade – 58 (77.3%) patients (95% CI, 66.9%-8.7%) which coincides with the data followed in women. Ischemic heart disease in

women and men in all severity grades coincides with the presence of hypertension. The occurrence of hypertension in gout may be associated with both the presence of traditional risk factors of hypertension and the influence of HU. Patients with cardiovascular comorbidities, and particularly with ischaemic heart disease, showed more severe gout outcomes expressed by medium to severe degrees of generalised inflammation with polyarticular developments. This was possibly due to the fact that most patients were on low-dose aspirin and associated diuretic (predominantly thiazide – Indapamide) therapy, which significantly aggravated HU and consequently the whole course of gout.

Kidney disease. In our study, the frequency of nephrolithiasis was twice as high in men with gout than in women: 174 (41.1%) men and 22 (28.2%) women, after ultrasound examination of patients with gout, the frequency of nephrolithiasis was 69.3% (Figure 3.9).

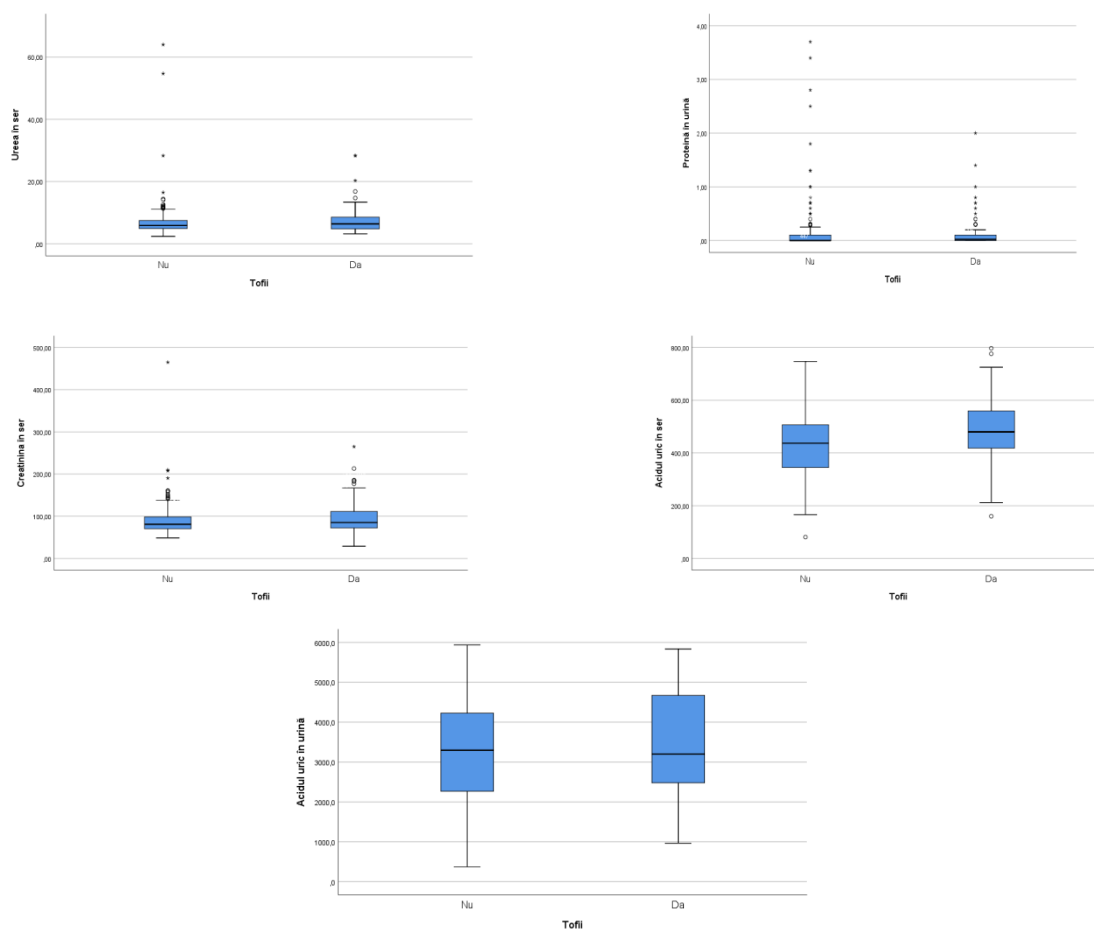


Fig. 3.9. Mean serum urea (a), proteinuria (b), serum creatinine (c), serum uric acid (d), uric acid in urine (e) and presence of tophi

The frequency of CKD detection in patients with gout followed in our study was 48%. It was observed that patients with gout and CKD were older, had a longer duration and a higher severity index of the disease, often had a chronic course compared to patients with gout without CKD. Kidney nitrogen excretory function decreased with patients' age and the duration of the disease increased. This decrease correlated with the severity index of gout and its components (number of affected joints, tophi and duration of last exacerbation), as well as with blood hemoglobin, C-reactive protein levels. In addition, there was a deterioration of kidney uricosuric function (daily uricosuria, clearance UA) in patients with

gout, correlating with patients' age, duration of gout, its severity index, presence of MS. An undesirable effect on the functional capacity of the kidneys, especially with its already existing disorders, according to our data, was also exerted by the administration of NSAIDs and colchicine chaotically and non-rationally. Similarly, we found that among the patients included in our study, according to modern concepts, the impairment of kidney function may also be due to the presence of hypertension, hyperlipidemia, type 2 DM.

Osteoarticular diseases. In our case study, a history of gouty attacks at individual joint sites was associated with the clinical presence of OA after adjusting for age, sex, BMI, and prior diuretic use. In particular, the first metatarsophalangeal joint, plantar, knee, and distal interphalangeal finger joint that was affected by gouty attacks were 2.1-fold, 2.9-fold, 3.1-fold, and 12.7-fold more likely to have concomitant OA that was clinically defined. Similarly, using the same dataset, we can report that joints affected by gouty arthritis were more likely to manifest chronic symptoms such as pain in OA. In our study OA in women was present – 63 (80.1%) of cases, with predominance in medium degree of severity (95% CI, 61.7%-87.9%), in men – 349 (82.5%) of cases, with predominance - medium degree of severity (95% CI, 77.4%-86.2%). We also examined the presence of psoriatic arthritis (PsA) – in women – medium degree is accompanied by PsA in 8 (14%) cases (95% CI, 6.9%-24.7%), mild degree – in 2 (11.1%) women (95% CI, 2.4%-31.1%) and one case of PsA in severe degree of gout. In men – APs, as in women – medium degree of severity of gout – in 24 (8.2%) men (95% CI, 5.5%-11.8%), severe degree – in 4 (7%) men (95% CI, 2.4%-15.8%). Degenerative spondyloarthritis, which was present in patients with gout, was found in men – 326 (77.1%), with predominance of medium degree of severity (95% CI, 75.9%-85.0%), in women – 62 (79.5%), also with predominance, as in men, medium degree of severity (95% CI, 65.1%-86.6%). Patients in our study had combination of osteoarticular diseases: gout+OA, gout+OA+APs, gout+OA+APs+degenerative spondyloarthritis or other combination of diseases influencing physical activity with decreased quality of life.

Administration and distribution of drugs according to severity grade in studied patients with gout: for the treatment of acute attack of gout, patients administered most often NSAIDs 378 (75.4%) patients with distribution according to severity grade – mild grade 70 (75.3%) patients (95% CI, 65.8%-83.2%), medium grade – 265 (76.1%) patients (95% CI, 71.5%-80.4%), severe grade – 43(71.7%) patients (95% CI, 59.4%-81.9%). Administration of glucocorticosteroids in 221 (44.1%) patients and colchicine in 220 (43.9%) patients was similar, with no statistical significance by severity grade. Glucocorticosteroids – mild grade – 38 (40.9%) patients (95% CI, 31.3%-51.0%), medium grade – 151 (43.4%) patients (95% I.I., 38.3%-48.6%), severe grade – 32 (53.3%) of patients (95% CI, 40.8%-65.6%). Colchicine – mild grade – 40 (43%) of patients (95% CI, 33.3%-53.2%), medium grade – 158 (45.4%) of patients (95% CI, 40.2%-50.7%), severe grade – 22 (36.7%) of patients (95% CI, 25.3%-49.3%). Patients received NSAIDs, glucocorticosteroids, colchicine as monotherapy or complex treatment – NSAID+colchicine, NSAID+perarticular infiltration with glucocorticosteroids or colchicine+perarticular infiltration with glucocorticosteroids, depending on the severity of gout (Figure 3.10).

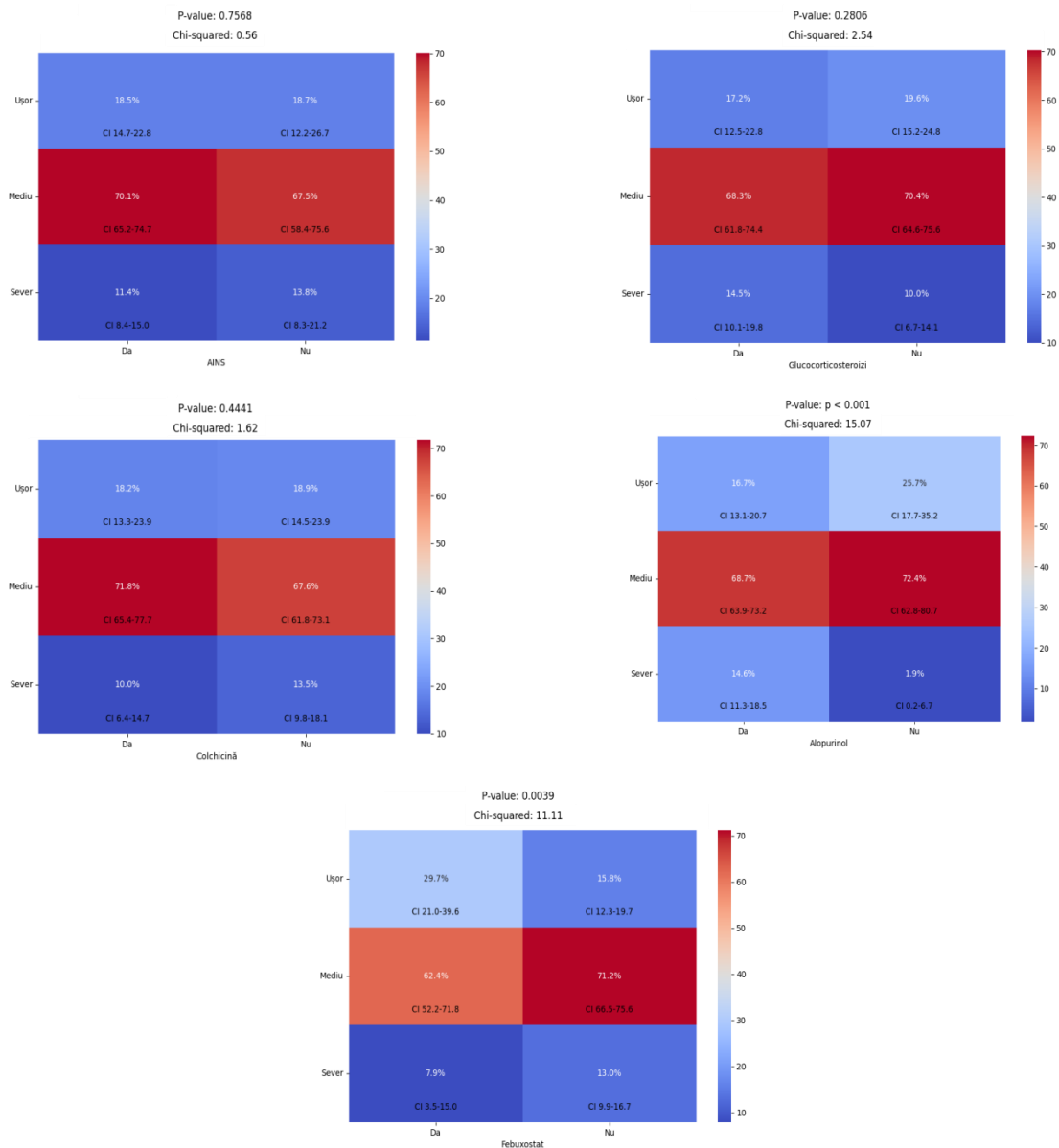


Fig. 3.10. Frequency of use of drugs (a - non-steroidal anti-inflammatory drugs, b - glucocorticosteroids, c - colchicine, d - allopurinol, e - febuxostat) in the complex treatment of gout according to the severity of clinical expression

From the group of drugs with uricostatic effect (xanthine oxidase inhibitors) two drugs are registered in Republic of Moldova – Allopurinol and Febuxostat. Allopurinol is 100% compensated and Febuxostat is partially compensated. We have observed a tendency towards the choice of drugs by patients, with the progression of comorbidities the number of drugs that the patient receives every day is increasing, because of this patients prefer drugs with 100% compensation. Treatment with allopurinol is more often used by patients with chronic tophaceous gout – 126 (31.8%) of patients (95% CI, 27.4%-36.5%) compared to febuxostat – 23 (22.8%) of patients (95% CI, 15.4%-31.6%). In nephrolithiasis the same situation is found – extensively administered allopurinol – in 164 (41.4%) of patients (95% CI, 36.6%-46.3%), but febuxostat – only in 47 (46.5%) of patients (95% CI, 37.0%-56.2%). In osteoarthritis

allopurinol administration is present in 334 (84.3%) of patients (95% CI, 80.5%-87.7%), but febuxostat - in 81 (80.2%) of patients (95% CI, 71.6%-87.1%).

4. COMORBIDITIES OF GOUT IN THE ELDERLY

4.1. Characteristics of elderly patients, provoking factors

Group II of elderly patients – 268 (53.5%) – represented a homogeneous group of patients aged 60-88 years. Most patients were aged between 60 and 71 years – 240 (89.5%) patients, from 72 to 88 years were 1 to 5 patients (Figure 4.1).

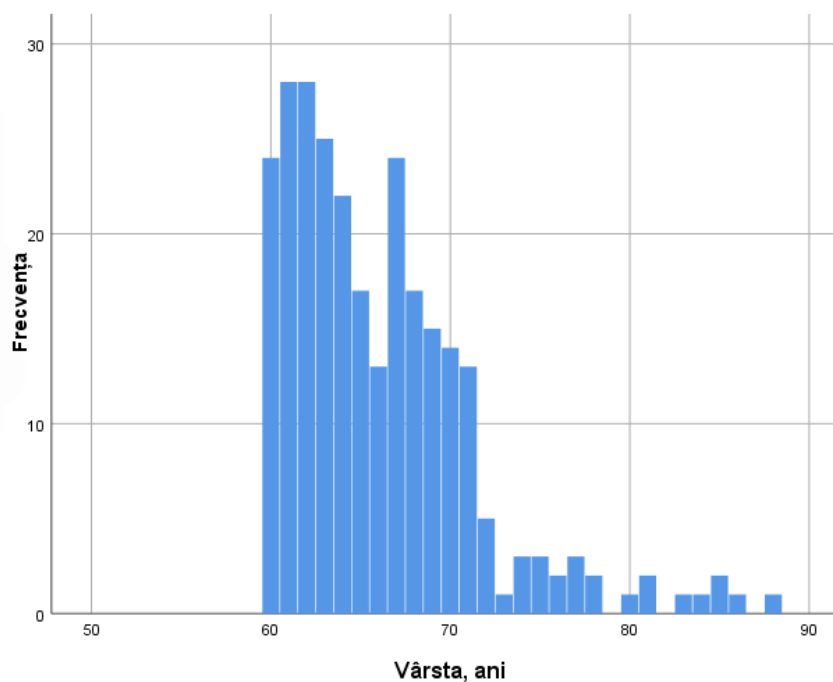


Fig. 4.1. Distribution of group II patients by age

Group II was dominated by men – 219 patients (81.7%) (95% CI, 76.8%-86.0%), compared to women – 49 patients (18.3%) (95% CI, 14.0%-23.2%). We compared group I – 233 (46.5%) patients with group II – 268 (53.5%) patients by severity of gout. In patients under 60 years of age, the medium severity of gout predominated – 120 (51.5%) patients (95% CI, 45.1%-57.9%), followed by cases with mild severity – 86 (36.9%) patients (95% CI, 30.9%-43.2%) and then – 27 (11.6%) patients (95% CI, 8.0%-16.2%) with severe grade of gout. In group II, also in the foreground are patients with medium degree of severity – 228 (85.1%) (95% CI, 80.4%-89.0%), but unlike group I, this is followed by patients with severe degree – 33 (12.3%) of patients (95% CI, 8.8%-16.6%) and mild degree being detected in only 7 (2.6%) patients (95% CI, 1.2%-5.1%).

The presence of tophi in patients with gout has also been associated with an increased risk of mortality. The basic clinical characteristics of tophi in these patients are summarized in Table 4.1, from which we can conclude that the presence of tophi was recorded in 27.6% of cases (74 patients), and their absence – in 72.4% of cases (194 patients).

Table 4.1. Distribution of elderly patients by presence of tophi

		n=268	%	95% CI, lower limit	95% CI, upper limit
Tophi	No	194	72.4	66.8	77.5
	Yes	74	27.6	22.5	33.2

Note: *II* - confidence interval; *n* - number of patients (absolute); % - number of patients in percent.

The frequency of tophus gout, comparable in both groups, was 45% in both groups I and II. The number of tophi at examination did not differ: 2.0 [0; 9.0] in group I and 2.0 [1; 4.5] in group II. The analysis of our study included the results of 268 patients (group II), people over 60 years of age, who had a chronic course of gouty arthritis and poor drug control of the disease. Metatarsophalangeal joint I was affected at the onset of gout in 140 (52.23%) patients (95% CI, 29.0%-75.0%), then the interphalangeal joints of the hands – in 33 (12.31%) (95% CI, 5.6%-14.2%) patients, the ankle joint in 29 (10.82%) (95% CI, 4.5%-11.0%) of patients, tarsal and metatarsal joints in 19 (7.08%) (95% CI, 2.4%-9.1%) of patients, knee joint in 17 (6.34%) (95% CI, 1.7%-3.1%) of patients, the interphalangeal joints of the feet in 16 (5.97%) (95% CI, 7.2%-12.5%) of patients, the radiocarpal joints in 14 (5.22%) (95% CI, 2.7%-6.7%) of patients. It was found, that more often in women was the onset of gout from the interphalangeal joints of the hands, tarsal and metatarsal, but in men – the I metatarsophalangeal joint, interphalangeal joints of the feet and ankle. After the progression of gout with chronic form, there were 95 (35.44%) (95% CI, 31.0%-47.9%) patients, of which 74 (27.61%) (95% CI, 21.4%-35.6%) patients with tophaceous form. Relapsing arthritis was present in 163 (60.82%) (95% CI, 51.1%-73.4%) of patients. Duration of gout at the time of examination was 11.2 years (range 8.02 to 16.3 years). The average number of exacerbations per year was 3 (range 2 to 6). The average height of elderly patients was 1.73±0.05 m, and the average body mass – 88.4±17.0 kg. Normal body mass was determined in 61 (22.76%) patients, and the mean body mass index was 29.7±5.4 (Table 4.2).

Table 4.2. Anthropometric data characteristics of elderly patients

Parameters	Average±SD	Median±SD	95% CI
Average height, m	1.73±0.05	8.14±1.09	0.845, 1.569
Average body mass, kg	88.4±17.0	179.5±24.8	1.421, 3.237
Average BMI, kg/m²	29.7±5.4	41.7±7.6	4.56, 8.389

Note: *BMI* – body mass index; *n* – number of patients (absolute); % – number of patients in percent; *SD* – standard deviation; *CI* – confidence interval.

Hereditary predisposition. The presence of a hereditary predisposition was observed significantly more often with the early onset of gout in group I – 41 (17.60%) of patients, than in group II – 12 (4.48%) of patients ($\chi^2=1.255$, $p=0.2625$). The results obtained may indicate the absence of influence of the hereditary predisposing factor on the risk of developing gout in the elderly. At the same time, burdened heredity is of greater importance for disease onset at a young age with progressive progression.

Administration of diuretics. Regular diuretic administration prior to gout onset was reported 2.5 times less in group I representatives than in group II representatives – 31 (13.3%) patients and 78 (29.1%) patients respectively, $p=0.0855$. The majority of patients who used diuretics in both group I and group II

before the onset of the first gout attack were on thiazide diuretics: 11.16% and 16.42% of those who received diuretics, respectively (Table 4.3). Loop diuretics were administered by 29 (10.8%) patients in group II, of whom five regularly received diuretics from both groups (Furosemide and Indapamide). The potassium-sparing diuretic (spironolactone) was taken by 5 patients in group II. Diuretics were prescribed by the doctor for combined treatment of hypertension or CHF.

Table 4.3. Administration of diuretics before onset of gout in both groups

Prepare	Group I (n=233)	Group II (n=268)	χ^2 , df=1, p
Diuretics in general, n (%)	31 (13.3%)	78 (29.1%)*	2.958, 0.0855
Loop diuretic group, n (%)	4 (1.72%)	29 (10.8%)*	0.321, 0.5711
Thiazide diuretic group, n (%)	26 (11.16%)	44 (16.42%)*	0.360, 0.5484
Both diuretic groups, n (%)	1 (0.43%)	5 (1.87%)*	0.009, 0.9245

Note: * $p < 0.05$; n – number of patients (absolute); % – number of patients in percent; χ^2 – coefficient of agreement; df – degree of freedom, p – coefficient of statistical significance according to the T-student criterion.

Administration of Acetylsalicylic acid. More than 6 times by frequency Acetylsalicylic acid was administered to group II representatives: 11 (4.7%) in group I and 34 (12.68%) in group II ($\chi^2=0.540$, $p=0.4623$). All those included in the study took Acetylsalicylic acid supplements, as prescribed by the doctor, in low doses (from 75 mg to 100 mg) in order to prevent cardiovascular disease complications, despite the fact that the validity of cardiovascular disaster prophylaxis provided by Acetylsalicylic acid decreases with age.

Drinking alcoholic beverages. It was observed that representatives of group I did not consult alcohol 19 (8.15%), of which men 9 (4.41%) and women 10 (34.48%) ($\chi^2=2.514$, $p=0.1129$), compared to group II – 60 (22.39%) where the increased level was recorded almost three times higher ($\chi^2=20.770$, $p=0.0001$). In group I, 53 (22.75%) of patients, of which 46 (22.55%) of males and 7 (24.14%) of females ($\chi^2=0.009$, $p=0.9262$), and in group II, 38 (14.18%) of patients, of which 33 (15.07%) of males and 5 (10.20%) of females ($\chi^2=0.081$, $p=0.7757$) consumed alcohol more times per year in group I than in group II. There were patients with alcohol consumption once a month: in group I 42 (18.02%) – men 38 (18.63%) and women 4 (13.79%) ($\chi^2=0.056$, $p=0.8135$) and in group II 63 (23.51%) – men 59 (26.94%) and women 4 (8.16%) ($\chi^2=0.680$, $p=0.4096$). Once a week 78 (33.48%) patients: men 72 (35.29%) and women 6 (20.69%) ($\chi^2=0.518$, $p=0.4716$) in group I and 67 (25.0%) patients: men 66 (30.14%) and women 1 (2.04%) ($\chi^2=0.367$, $p=0.5447$) in group II consumed alcohol, about 90% were men than women. Of the total number of patients included in the study, frequent consumption of alcoholic beverages (once a week and more often) in group I – 41 (17.59%) patients, of which – men 39 (19.12%) and women 2 (6.89%) ($\chi^2=0.184$, $p=0.6680$). At the same time, in group II – 40 (14.92%) of patients: men – 36 (16.44%) and women 4 (8.16%) ($\chi^2=0.183$, $p=0.6691$).

Eating foods high in purines. Consistent use of purine-saturated foods was observed significantly more often in group II – 156 (58.21%) patients compared to 49 (21.03%) patients in group I, ($\chi^2=20.521$, $p=0.0001$), while there were no significant sex differences in group I – 37 (15.88%) males and 12

(5.15%) females ($\chi^2=0.889$, $p=0.3458$), but in group II there were significant sex differences – 130 (48.51%) males and 26 (9.7%) females ($\chi^2=13.307$, $p=0.0003$).

Hypertension. Hypotensive therapy was administered to about half of the patients with a history of hypertension at the time of gout onset: 48 (20.6%) of patients in group I and 117 (43.66%) of patients in group II ($\chi^2=7.722$, $p=0.0055$). In group I, 31 (13.3%) patients received diuretics, in group II – 38 (14.18%) patients received diuretic antihypertensive treatment ($\chi^2=0.011$, $p=0.9166$) (Table 4.4).

Table 4.4. Antihypertensive therapy with onset of hypertension before onset of gout, years

Parameters	Group I (n=233)	Group II (n=268)	χ^2 , df=1, p
Received antihypertensive therapy, n (% of total number of patients with hypertension)	48 (20.6%)	117 (43.66%)	7.722, 0.0055
Including diuretics, n (% of total number of patients with hypertension)	31 (13.3%)	38 (14.18%)	0.011, 0.9166

Note: * $p<0.05$, n – number of patients (absolute); % – number of patients in percent; χ^2 – coefficient of agreement; df – degree of freedom, p – coefficient of statistical significance according to the T-student criterion.

The data demonstrate a link between the unusually early development of hypertension and the early onset of gout. The mean age of onset of hypertension in group I patients is significantly lower than the age of the population, indicating the need to include young patients with hypertension in the risk group for developing gout. It may also indicate early gouty renal lesions with symptomatic hypertension formation long before the manifestation of joint syndrome. Long-term use of diuretics as antihypertensive therapy may be an additional factor contributing to the development of gout in patients with hypertension.

Obesity. Overweight and obesity (BMI – 25-29.9 kg/m² and BMI equal to and greater than 30 kg/m², respectively) were observed with comparable frequency among representatives of both groups ($p=0.19$). Overweight in group I were in 64 (27.47%) of patients and 79 (29.47%) of patients in group II ($\chi^2=0.069$, $p=0.7931$). Obesity was in 69 (29.61%) of patients in group I and 57 (21.26%) of patients in group II ($\chi^2=1.127$, $p=0.2884$) (Table 4.5).

Table 4.5. Overweight and obesity in patients with gout

Nosology	Group I (n=233)	Group II (n=268)	χ^2 , df=1, p
Overweight, n (%)	64 (27.47%)	79 (29.47%)	0.069, 0.7931
Obesity, n (%)	69 (29.61%)	57 (21.26%)	1.127, 0.2884
Overweight and obesity before onset of gout, n (%)	90 (38.6%)	99 (36.9%)*	0.058, 0.8172

Note: * $p=0.05$; n – number of patients (absolute); % – number of patients in percent; χ^2 – coefficient of agreement; df – degree of freedom, p – coefficient of statistical significance according to the T-student criterion.

The presence of overweight or obesity before the onset of gout was observed in a significantly higher number of cases in group II: 90 (38.6%) in group I and 99 (36.9%) in group II ($\chi^2=0.058$, $p=0.8172$). In group I patients, weight gain occurred at a younger age – up to 40 years – in 56 (62.2%) and in group II patients in 28 (28.86%) ($\chi^2=0.211$, $p=0.6464$). In group I there were 14 (15.5%) patients, compared to group II 45 (45.45%) ($\chi^2=3.983$, $p=0.0460$) patients who reported the onset of obesity in the

period after 40 years. In 18 (20%) patients in group I, overweight or obesity occurred before the age of 20 years, which was observed in group II in only one patient (1%) ($\chi^2=0.211$, $p=0.6464$). After 60 years of age, in group I patients, the occurrence of weight disorders occurred in only 2 (2.2%) patients, and in group II – 25 (25.77%) patients ($\chi^2=0.543$, $p=0.4613$). The findings confirm the significant role of overweight as a factor in the development of gout: in most cases, in young, middle-aged and elderly patients, obesity immediately preceded the onset of gout, and the earlier development of obesity was associated with a decrease in the age of disease development.

Chronic kidney disease. Despite its predictive role in the development of gout, CKD was present prior to onset in only 5 patients (2.14%) in group I and 9 (3.36%) patients in group II ($\chi^2=0.016$, $p=0.9004$). The mean age at diagnosis of CKD was 45 ± 3 years in group I and 54 ± 4 years in group II. In the early stages of CKD, when the glomerular filtration rate is not less than 60 ml/min/1.73 m², as usual, these patients do not show clinical symptoms. We can assume that the actual number of patients with CRB before the onset of gout is higher than the data mentioned.

Age of onset of comorbidities. Patients with gout had a pronounced comorbid background. Most had 2-5 comorbidities. The mean number of comorbidities of gout was 3.8 ± 1.5 . The frequency of comorbidities (hypertension, ischemic heart disease, chronic heart failure, nephrolithiasis, chronic kidney disease, type 2 diabetes) in patients included in the study naturally increases with age, which generally shows a significantly higher comorbid background at older ages. In group I, before the onset of gout, frequent pathology was hypertension in 71 (30.47%) patients, then in decreasing order, nephrolithiasis was present in 24 (10.3%) patients, ischemic heart disease – 22 (9.44%) patients, type 2 diabetes mellitus – 8 (3.43%) patients, chronic heart failure – 7 (3.0%) patients, chronic kidney disease – 5 (2.14%) patients. In, comparison with group II, after hypertension, which also ranked first – 42 (15.67%) of patients, was ischemic heart disease – 28 (10.44%) of patients and concluded – type 2 diabetes mellitus - 7 (2.61%) of patients (Table 4.6).

Table 4.6. Frequency of pathological conditions before onset of gout

Nosology	Group I (n=233)	Group II (n=268)	χ^2 , df=1, p
Hypertension, n (%)	71 (30.47%)	42 (15.67%)	3.058, 0.0803
CPI, n (%)	22 (9.44%)	28 (10.44%)*	0.013, 0.9078
ICC, n (%)	7 (3.0%)	14 (5.22%)*	0.051, 0.8210
Nephrolithiasis, n (%)	24 (10.3%)	17 (6.34%)*	0.193, 0.6608
CKD, n (%)	5 (2.14%)	9 (3.35%)*	0.015, 0.9012
Type 2 DM, n (%)	8 (3.43%)	7 (2.61%)*	0.008, 0.9290

Note: * $p<0.05$; ICC – ischemic heart disease; CHF – chronic heart failure; CKD – chronic kidney disease; T2DM – type 2 diabetes mellitus; n – number of patients (absolute); % – number of patients in percent; χ^2 – coefficient of agreement; df – degree of freedom, p – statistical significance coefficient according to T-student criterion.

The mean age of development of diseases preceding the onset of gout was different (Table 4.7). Significantly earlier onset of hypertension was observed – in group I at age 36.9 ± 5.8 years, compared to group II – 53.9 ± 7.1 of ($p<0.05$). In group I, the mean age of manifestation of ischemic heart disease is 50.1 ± 6.9 years, and in group II – 57.7 ± 3.4 years, ($p<0.05$). Diagnosis of CHF was established before the

development of gout in group I patients at mean age 54.8±5.1 years and at mean age 66.8±9.1 years in group II; age of development of CHF was significantly lower in group I ($p<0.05$). The mean age of nephrolithiasis development in group I was 42.2±6.5 years and lower than the mean age of nephrolithiasis onset in group II – 54.2±11.1 years ($p<0.05$). CKD diagnosis was established before gout development at mean age of 46.9±5.2 years in group I and at age of 61.2±8.52 years in group II. The mean age of detection of type 2 DM did not differ significantly between groups.

Table 4.7. Average age of development of diseases preceding the onset of gout

Age of debut	Group I (n=233)	Group II (n=268)
	Average±SD	Average±SD
Gout, years	43.1±7.2	64.9±3.8*
Hypertension, years	36.9±5.8	53.9±7.1*
Ischemic heart disease, years	50.1±6.9	57.7±3.4*
Chronic heart failure, years	54.8±5.1	66.8±9.1*
Nephrolithiasis, years	42.2±6.5	54.2±11.1*
Chronic kidney disease, years	46.9±5.2	61.2±8.5
Type 2 diabetes mellitus, years	51.1±3.3	54.8±5.4

Note: * $p<0.05$; n – number of patients (absolute); % – number of patients in percent; SD – standard deviation.

A renal function analysis was performed at the time of examination. In group I, median blood creatinine values did not correspond to normal parameters in men and women, exceeding normal values, and median urine total protein values were higher than optimal. In group II, median values of serum creatinine in both men and women, total urine protein were significantly higher than in group I, while exceeding reference values. Significantly lower than in group I, a mean GFR value was shown at late onset of gout. In group I, the median GFR corresponded to a normal value, in group II it showed a decrease in renal function. A significantly higher number of patients in group II had stage IV CKD – 17 (6.34%). We can conclude the fact of a more severe evolution of gout in patients over 60 years of age, which is characterized by a clinical damage of the kidneys with the development of their malfunction – expressed by increased serum urea concentration, creatinine and proteinuria.

Earlier development of chronic non-communicable diseases associated with gout (hypertension, ischemic heart disease, CHF, nephrolithiasis, CKD) is accompanied by its earlier onset. In addition to pathogenetic associations, therapy with drugs that are usually considered risk factors for gout – Acetylsalicylic acid, diuretics – may also play a role in their development. Also, CKD, nephrolithiasis and hypertension may be directly related to gouty nephropathy, preceding the onset of arthritis.

Characteristics of gout onset by age. The first metatarsophalangeal joint onset in 173 (74.25%) patients in group I was significantly higher than in group II patients – 140 (52.23%) cases ($\chi^2=16.313$, $p=0.0001$). Damage to other joints of the lower extremities occurred with the following comparable frequency in both groups: ankle joints: in group I 22 (9.44%) of patients and in group II 29 (10.82%) ($\chi^2=0.025$, $p=0.8733$). Knee joints were affected: in group I – 14 (6.0%) patients, in group II – 17 (6.34%)

patients ($\chi^2=0.001$, $p=0.9693$). Tarsal and metatarsal joints were affected at gout onset in group I – 11 (4.72%), in group II – 19 (7.08%) ($\chi^2=0.064$, $p=0.7997$). The interphalangeal joints of the feet were affected in group I – 7 (3.0%), in group II – 16 (5.97%) ($\chi^2=0.085$, $p=0.7701$). Rarely, gouty inflammation started in the radiocarpal joint – in 2 (0.86%) patients in group I and more often in group II – 14 (5.22%) ($\chi^2=0.070$, $p=0.7914$) patients. Significantly more often, gout resulted in damage to the interphalangeal joints of the hands in patients in group II: 12.31% compared to 1.72% in group I ($\chi^2=0.070$, $p=0.7914$). Chronic progression of arthritis was initially appreciated in 12 (4.48%) patients in group II, while in group I initial chronicity of the gout process was observed in 4 (1.72%) patients. A shorter period of time elapsed before chronic disease progression in group II: in 103 (38.43%) ($\chi^2=6.915$, $p=0.0085$) patients chronic arthritis appeared 2-5 years after the onset of gout, whereas in group I this period lasted between 6 and 10 years. After 6 years, chronic arthritis was established in – 81 (30.22%) patients in group II, compared to group I – 67 (28.75%) patients ($\chi^2=0.038$, $p=0.8458$). In group I, 10 years elapsed from onset to onset of chronic arthritis in 40 (17.16%) patients, while in group II, a long period of chronic arthritis development was noted in 36 (13.43%) patients ($\chi^2=0.200$, $p=0.6549$). The number of joints affected during the disease and of swollen joints at the time of examination was comparable in both groups (median joints affected during the disease in group I – 1.5 [6.0; 20], in group II – 10 [5.0; 20], $p=0.8$ (Figure 4.2). The median of swollen joints at the time of examination in group II was 0.5 [0.0; 2.0], in group I – 1.0 [0.0; 4.0], ($p=0.6$). The frequency of arthritis attacks in the recurrent course of gout also showed no significant differences between groups: 4.0 [2.0; 6.0] in group I and 3.0 [2.0; 4.0] in group II ($p=0.1$).

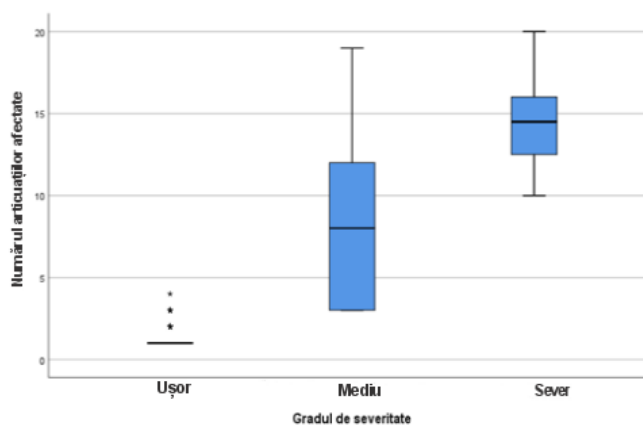


Fig.4.2. Average severity of gout and number of joints affected

Statutory data of patients included in the study: mean height in group I – 1.75 ± 0.07 , in group II – 1.73 ± 0.05 . Mean body mass in group I were 92.5 ± 20.4 , in group II – 88.4 ± 17.0 , which corresponds to BMI equal and greater than 25 kg/m^2 , in more than 80% of patients in both groups ($p=0.06$).

4.2. Comparative analysis of comorbid diseases in elderly and adult patients

Based on the premise of analysing comorbidities, there is a clear need for specific questionnaires that could quantify the presence of comorbidities. One such questionnaire is the Charlson Comorbidity Index, a popular tool for risk adjustment, but with some limitations due to patient self-report as an

alternative and, more over, there is little data on whether self-reported Charlson indices predict mortality. Thus, according to literature data, self-reported Charlson indices predict mortality at 1 year, comparable to indices based on administrative data, for which reason we did not consider it appropriate to use this index in this study, as we did not aim to analyse mortality or aggressiveness of the treatment administered. Significantly more frequently in group II patients were determined hypertension in 228 (45.5%) patients, ischemic heart disease in 222 (44.3%) patients, compared to group I – hypertension - in 184 (36.7%) patients, ischemic heart disease – in 168 (33.5%) patients. According to the presence of severity grade – in both groups, ischemic heart disease and hypertension, the most, were present in patients with medium grade. Taking into account the presence of a much higher rate of metabolic syndrome manifested among patients over 60 years of age, following the statistical analysis we obtained the expected results on cardiovascular pathology: increased rate of patients with ischemic heart disease and hypertension. However, it is necessary to mention that hypertension also showed conjugations with renal dysfunction. The cumulative severity grades of ischaemic heart disease (Figure 4.3a) and hypertension (Figure 4.3b) were definitely increased among patients aged over 60 years.

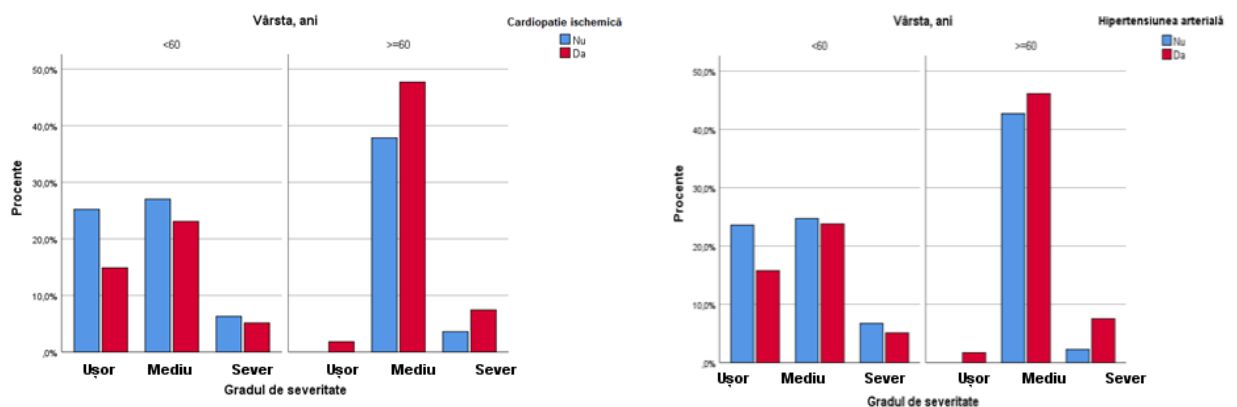


Fig. 4.3. Severity of gout and presence of ischaemic heart disease (a) and hypertension (b)

Type 2 DM was determined in a comparable number of cases between groups. It is worth mentioning the significantly higher proportion of medium – form type 2 DM (Figure 4.4) among patients over 60 years of age, which, likewise, fits into the metabolic syndrome along with hepatic steatosis (Figure 4.5) and dyslipidaemia. This demonstrates a significant disruption of overall metabolism with deregulation of all links of homeostatic balance.

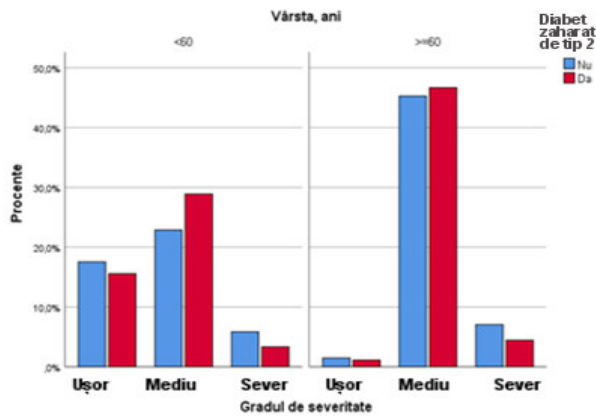


Fig. 4.4 Degree of expression of type 2 diabetes mellitus in patients included in the study

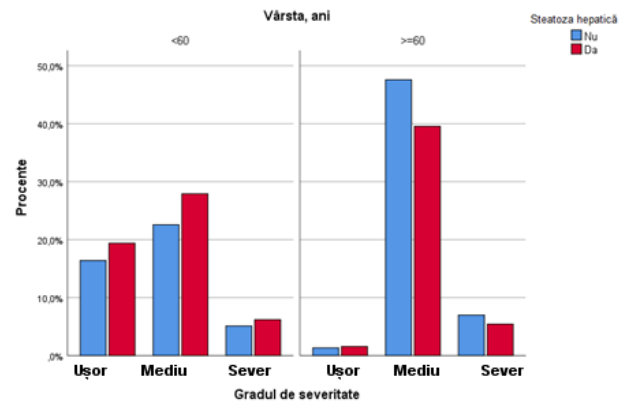


Fig. 4.5 Severity of hepatic steatosis expression according to the age of the patients included in the study

Chronic tubulointerstitial nephropathy (Figure 4.6a) was present in group I with mild grade of gout in 47 (54.7%) of patients, 64 (53.3%) of patients with medium grade of gout and 22 (81.5%) of patients with severe grade of gout, compared to group II – majority of patients were in medium grade of gout - 155 (68%) of patients. Nephrolithiasis (Figure 4.6b) was also determined with the same rate of cases in more than 70% of the representatives of each group. It is worth mentioning a significant frequency of renal disease in both groups of patients - which proves the major toxicity of HU on the kidney. Cumulatively, renal pathology expressed by bilateral chronic tubulointerstitial nephropathies was more frequent in patients over 60 years of age and, as a consequence, we note a definitely increased incidence of nephrolithiasis with predominance of medium and severe clinical forms.

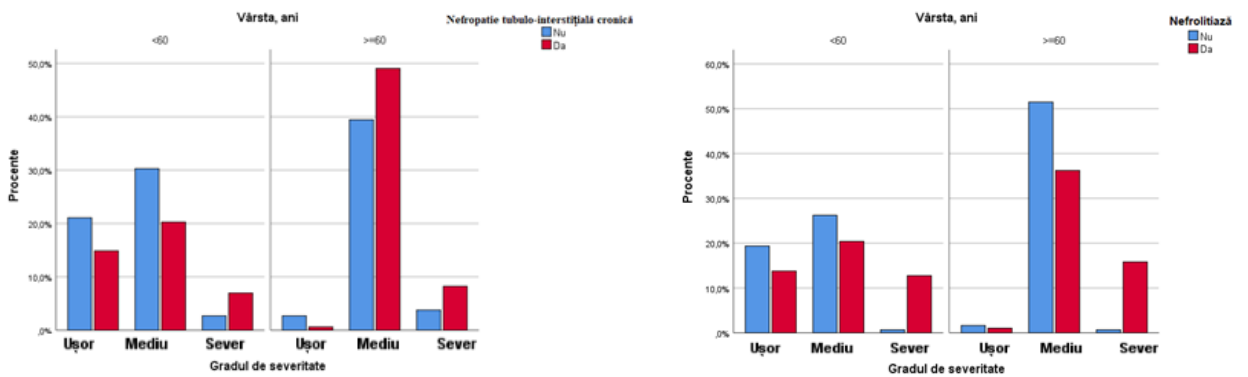


Fig. 4.6 Frequency of clinically expressed forms of tubulointerstitial nephropathy and nephrolithiasis in the age groups of patients included in the study

It is necessary to note the wide association of comorbid joint diseases in the patients included in the study, the most frequently detected being: psoriatic arthritis, degenerative spondylopathies and osteoarthritis. A predictable fact for us was the increased incidence of psoriatic arthritis overall in the study group, causing concomitant worsening of purine metabolism and consequently gout. In patients over 60 years of age, psoriatic arthritis predominated in the medium and severe forms of gout (Figure 4.7). An expected fact – considering the pathogenesis of the diseases - was the increased incidence of degenerative spondylitis (Figure 4.8) and osteoarthritis (Figure 4.9) in elderly patients with gout. Among

patients with onset of gout in the interphalangeal joints of the hands, in 3 women in group II, gouty joint lesions were simultaneously associated with interphalangeal joint lesions.

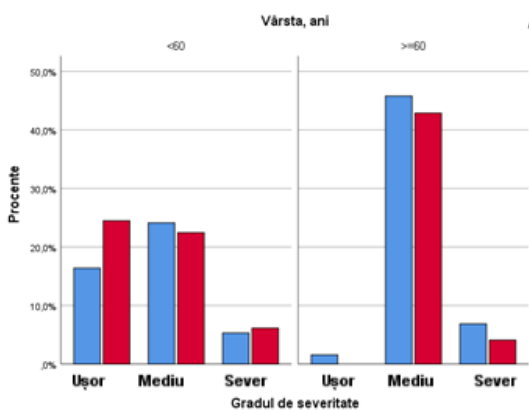


Fig. 4.7 Frequency of clinical forms of psoriatic arthritis in patients included in the study

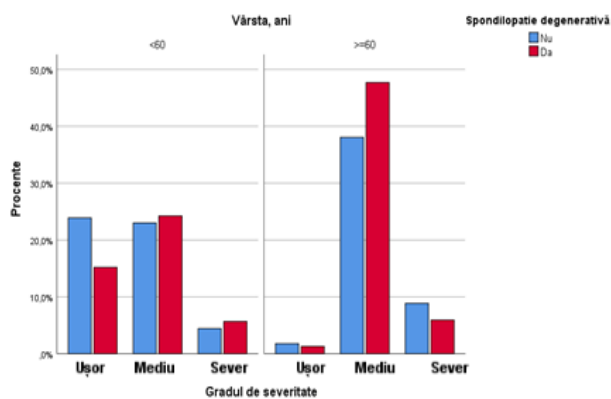


Fig. 4.8. Frequency of clinical forms of degenerative spondylitis in patients included in the study

In elderly patients, the chronicity of the gout process occurred earlier. The clinical manifestation of the onset of gouty arthritis does not differ significantly by age, which may help in the early diagnosis of gout in elderly patients. Attention should be paid to the more frequent localization of gouty arthritis in the area of the small hand joints in elderly patients, which requires differential diagnosis with OA.

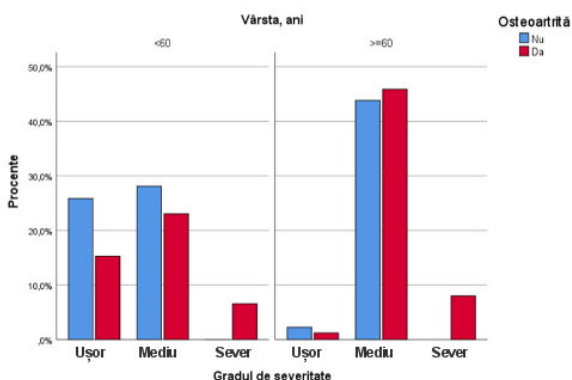


Fig. 4.9. Frequency of clinical forms of osteoarthritis in patients included in the study

The mean number of comorbidities was twice as high in group II 2.0 [2.0; 3.0] and 4.0 [3.0; 5.0], respectively ($p < 0.1$). Only 2 (1%) patients in group I had no comorbid pathology: both were male, aged 56.7 years at the time of examination, with onset at 47.1 years, and aged 37.6 years at the time of examination, with onset at 28.1 years. The highest number of patients in group I had two comorbidities in 25 (35.2%) patients. In group II, 58% had four or five comorbidities. One patient in group I and 8 in group II had all 6 comorbid gout diseases. Separately, the variants and frequency of the combination of comorbid diseases in the representatives of groups I and II were considered. In group I, the combination of hypertension and nephrolithiasis was significantly prevalent in 17 patients (23.9%), in 10 patients (14.1%) gout was accompanied by hypertension, nephrolithiasis and type 2 diabetes mellitus; 7 patients had only nephrolithiasis and 6 – only hypertension. In 4 patients (5.6%) a combination of gout and hypertension, ischemic heart disease, nephrolithiasis and type 2 DM was determined. Other comorbidities

identified in group I occurred less frequently than 5%. In group II, the most frequent cases followed up were combinations of gout with hypertension, ischaemic heart disease, CHF, nephrolithiasis and type 2 DM – 19 (15%) patients, in a significant number of patients, gout being combined simultaneously with hypertension, ischaemic heart disease, CHF, nephrolithiasis and CKD – 15 (12%) patients. In 11 (8.5%) patients a combination of gout simultaneously with hypertension, ischemic heart disease, CHF, nephrolithiasis was observed, in 9 (7%) patients – with hypertension, ischemic heart disease, CHF and in 9 (7%) patients gout was combined with hypertension, ischemic heart disease, nephrolithiasis, chronic renal failure. In 8 cases hypertension and ischemic heart disease were determined as comorbid diseases, and in 7 cases – hypertension and nephrolithiasis. All other combinations of comorbid diseases were determined with a frequency of less than 5%. Options for combinations of the most frequent (in more than 50% of cases) comorbidities in groups were considered. The most frequent combination followed in the representatives of group I was between hypertension and nephrolithiasis (78.8%). In group II the combination of gout with hypertension and ischaemic heart disease (82.9%), with hypertension and nephrolithiasis (72%), with hypertension, ischaemic heart disease and nephrolithiasis (58.9%). Widely represented in different combinations of concurrent pathology in both groups and, at the same time, isolated cases of detection of gout without or with concurrent disease of both young and old age indicate comorbidity as an integral part of gout.

In the inpatient treatment, NSAIDs were used extensively, from group I – 176 (35%) patients and from group II – 202 (40.3%) patients and in both cases – in medium severity of gout (Figure 4.10).

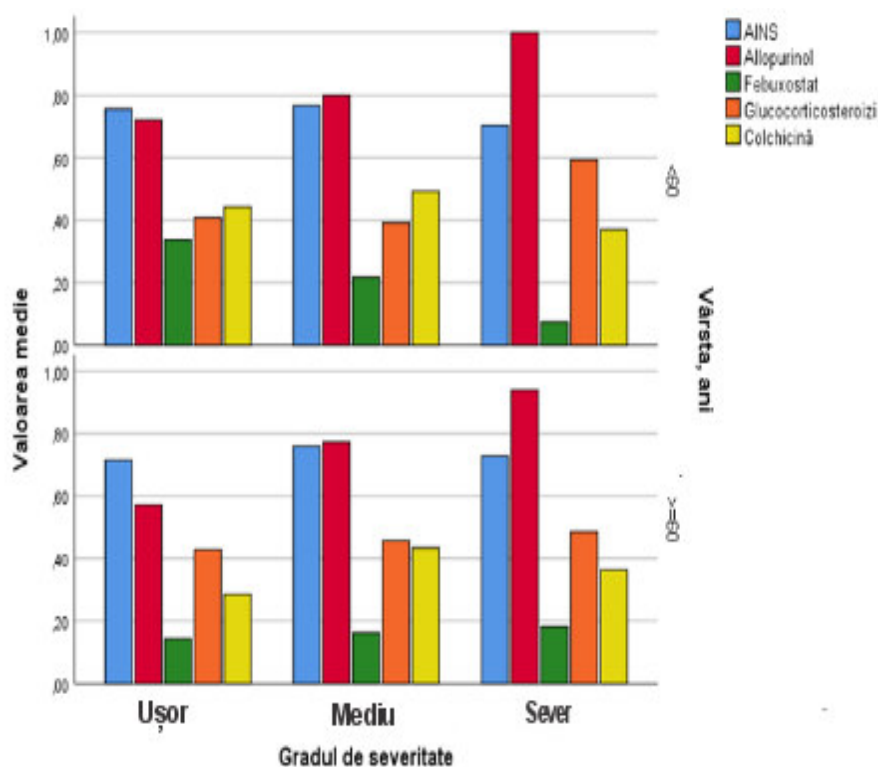


Fig. 4.10. Comparison of drug administration according to severity of gout and age of patients

Glucocorticosteroids were administered – in group I – to 98 (19.5%) patients, in group II – to 123 (24.5%) patients, more often by patients in group II, in the medium degree of severity of gout – 104 (45.6% of 268 patients) (95% CI, 39.2%-52.1%), most often in the form of injections with intra – or periarticular infiltrations into the affected joints. Colchicine was administered in both groups: in group I – in 107 (21.3%) patients, in group II – in 113 (22.5%) patients (Figure 4.10).

In outpatient treatment with uricodepressant drugs in the patient groups, allopurinol was administered more often – 185 (37%) patients in group I and 211 (42%) patients in group II, than febuxostat – in group I – 57 (11.4%) patients, in group II – 44 (8.8%) patients. Allopurinol is compensated 100% by the National Health Insurance Company (NHIC), patients receive it free of charge as part of the treatment prescribed by the family doctor, but febuxostat is partially compensated, and this fact influences the patient's choice, taking into account that with age the number of nosologies increases, which still provide for the procurement of drugs.

5. COSTS OF TREATING AN ELDERLY PATIENT WITH GOUT

5.1. Calculation and analysis of the direct costs of providing care to patients with gout by age and co-morbidity

In calculating the direct medical costs of treating a patient with gout, taking into account comorbid diseases according to the standards of medical care for patients with gout, hypertension, ischaemic heart disease, CHF, nephrolithiasis, CKD, type 2 DM, tariffs for medical services provided under the national compulsory medical insurance scheme were used.

The aim of this paper is to report the costs of a large sample according to NCPs used in the treatment of patients with gout, taking into account not only the main disease but also comorbidities, considering the elderly, describing in detail the technical functions of TCAT and illustrating the use of this costing tool. For the calculations, the hospitalization rate during the year (K) was used, which had significant differences in the groups: in group I it was 0.9; in group II – 1.4, ($p=0.001$). The costs of treating gout and each of the accompanying diseases for 1 calendar year were determined. It was assumed that the cost of outpatient treatment of each disease for one year according to the NCP was the same in the groups. The most expensive outpatient treatment of type 2 DM was 3.5 times the cost of inpatient treatment in group I (78% and 22% of total costs, respectively) and 2 times in group II (67% and 33%, respectively), which is due to the peculiarities of medical care for this disease: relatively expensive treatment received on a consistent basis and the absence of surgical manipulation or other high-tech inpatient care. Among other comorbidities, with the exception of type 2 DM, the cost of outpatient and inpatient treatment in group I was correlated as 1:7 – 13% of the cost of treating the disease, on average, accounted for outpatient care provision and 87% for inpatient care provision. In group II, the cost of inpatient care was slightly higher than in group I, with a higher incidence of inpatient treatment (on average, excluding type 2 DM, 8% of total medical care accounted for outpatient care and 92% – inpatient care). The most costly was inpatient treatment of CKD and ischaemic heart disease. The value of this amount was influenced by: significant duration of inpatient treatment (30 days); provision of

specialized, high-tech care according to the standards used (imposition of anastomoses on coronary vessels in ischemic heart disease, haemodialysis, plasmapheresis in CKD); significant amount of medical services provided according to the NCP.

5.2. Assessing the costs per case treated on an ongoing basis and developing principles to streamline expenditure in line with developments

Obviously, in the treatment of several diseases at the same time, occurring with high comorbidity in patients with gout, some services will simultaneously meet several standards: a general blood test, urine, biochemical analysis, recording and description of an electrocardiogram and others. These medical services can be considered as general costs (GC). An analysis of the costs of treating gout and related diseases shows that CG represents between 5.5% and 29.5% of the total cost of treating each disease per year. The most significant amount of CG includes the cost of providing care for gout, hypertension, CHF and CKD (Figure 5.1). To calculate the cost of treating a conditioned patient for 1 year, taking into account comorbid pathology, it was proposed to use a decreasing marginal coefficient. The coefficient is non-linear in nature, its value was empirically derived and entered into the Nomenclature of Health Works and Services in 2017.

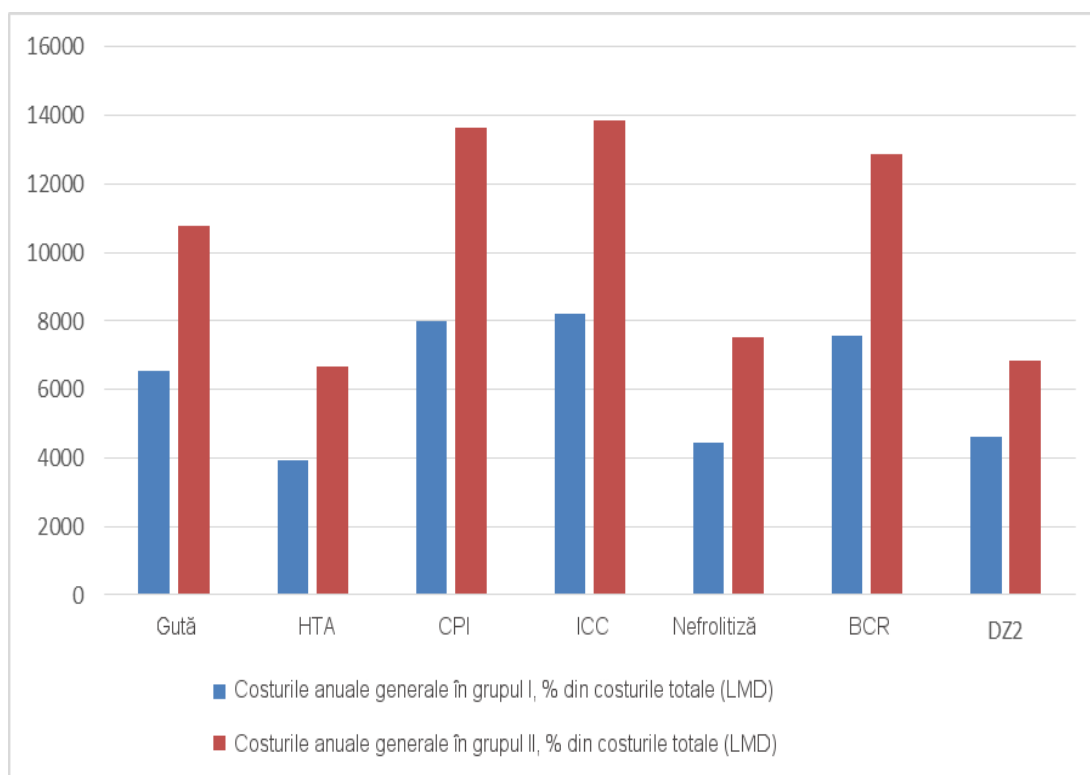
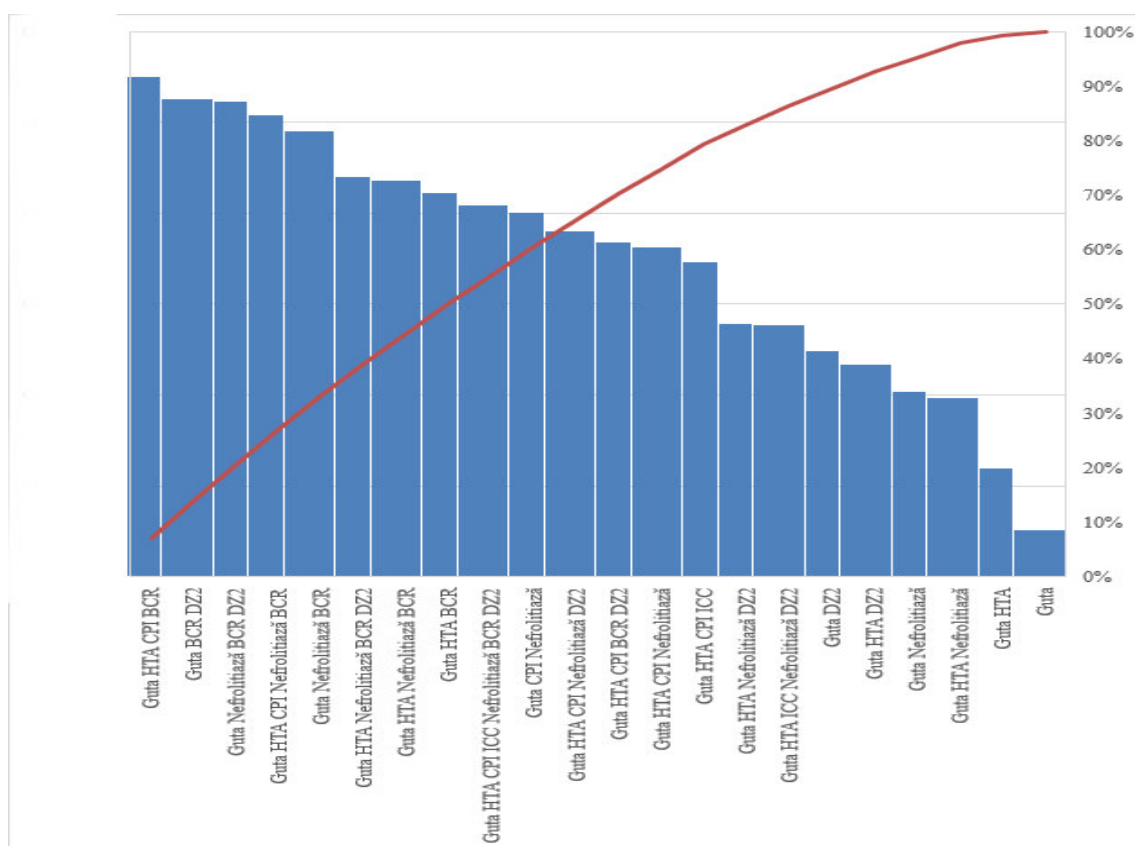


Fig. 5.1. Overall costs for one year of outpatient treatment combined with a single period of inpatient treatment, LMD

The need to apply the marginal coefficient in the presence of comorbidity can be justified by comparing different calculation methods: without and using this coefficient. For example, in a patient with gout who has five comorbid diseases, aged over 60: hypertension, ischaemic heart disease, CHF, nephrolithiasis and type 2 DM (Figure 5.2). When calculating costs according to the first method

(calculating the cost of treating the patient by including the sum of the cost of treating each disease), the amount obtained significantly exceeds the real possible costs, because the GCs associated with general medical examinations, handling and implementation of patient care, set out in each standard, are summarised, despite the fact that in reality they are produced only once and distort the result. When summarising all costs of treating five diseases except gout, the total projected costs per patient for one year are 423 508 LMD. With the introduction of the marginality factor, the projected costs are only 254 105 LMD. The costs of treating gout and comorbid diseases for each available combination of comorbid pathology in Group I and II representatives. The TCAT (Treatment Cost Analysis Tool) is also distinctive in that it incorporates analysis directly into the tool, making it an analytical tool rather than simply a data collection device. It relies on the built-in facilities of spreadsheet software for mathematical calculation and graphical presentation to automate the cost analysis process.



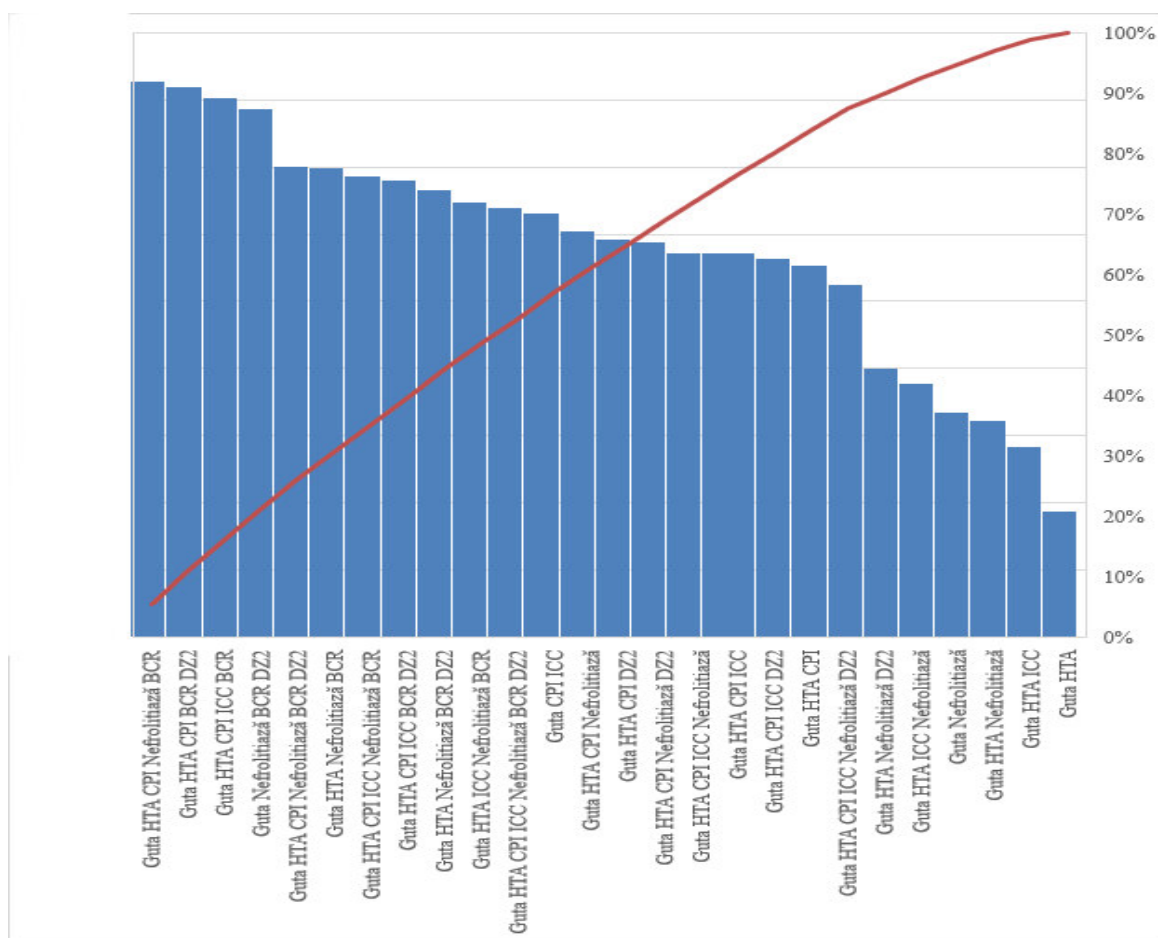


Fig. 5.2. Costs of treating gout in combination with comorbid diseases for 1 calendar year in group I (a) and group II (b), taking into account marginality, LMD

The Pareto chart shows the distribution of data in descending order of frequency.

The cumulative value line on the secondary axis shows the rate of the total.

Calculation of the average treatment costs of patients with gout, taking into account concurrent pathology in groups I and II, showed that their main volume decreases with comorbid diseases and increases significantly with age. The results make it possible to determine the real costs of treating a patient with gout, significantly exceeding the costs of treating the underlying disease. The cost of treating gout itself in group II was 1.5 times higher than the costs in group I. Taking concomitant pathology into account, the costs in patients under 60 were 5.4 times higher, and in those over 60 – 7.4 times. The increased cost of treating gout in the elderly is associated with an increase in the volume of hospital care and the number of comorbidities. Since lack of AU control leads to increased severity of gout and accumulation of comorbidities, maintaining AU at a normal level not only leads to a better prognosis, but also to a more economically profitable one. The per case costs of inpatient care for elderly patients with gout, as determined by PCN tariffs using DRGs, and actual costs differ significantly, leading to the need for further improvement and optimisation. According to the methodological basis of the cost-based approach used in the ADSS (Alcohol Drug Services Study), we can conclude that TCAT (treatment cost analysis tool) contributes to the transformation towards a reasonable choice for cost assessment in future large-scale studies. The ADSS is based on a relatively short and flexible instrument. The short length

meant giving up some details, but that may be an appropriate compromise when working with a large sample [8, 9]. Compared to the original ADSS tool, the TCAT extends the coverage of some cost components, especially in terms of non-personnel costs and administrative costs. However, it retains much of the flexibility and computational elements of the original, which will serve to make TCAT useful in many of the same situations [8, 9]. Another future direction is the use of an Internet version designed to approximate an interview format, similar to commercially available tax preparation software. Online applications offer several advantages, including wider access, centralized data capture, and ease of maintenance and updates. An undoubted strength is the ability to customize and streamline the user experience to facilitate the data capture process. The virtual version of TCAT (TCAT-I) addresses this challenge by displaying only as many input rows as possible, because the program includes staff members using drop-down lists to assist with data entry. Thus, TCAT-I can obtain more convenient details. Recognizing that cost analysis is the first step in economic evaluations and “only a partial form of economic evaluation” [8, 9], TCAT provides the opportunity to develop the data sets needed to conduct separate and subsequent economic investigations (e.g., cost-effectiveness ratio, cost function analysis, etc.). Indeed, such analyses have already been performed by TCAT and its predecessor CDAI (e.g., see) [8, 9]. Nor is the need for economic evaluation unique to the state. National or subsidized treatment systems must also allocate their budget in a way that best supports outcomes, which may require monitoring and cost containment. TCAT is available for use outside the USA or Canada, with the caveat that adaptations may be required depending on funding mechanisms, cost centers, and other treatment system differences that may not correspond to current practice in US dollars, but these costs can easily be converted to other currencies – for example, euros or leu Moldova, according to the National Bank's exchange rate. However, the ways in which the polypragmacy screening services are different from those in the USA, TCAT applications in countries other than the US require changes in the scope of the tool, but some of the technologies and methodologies (e.g. consistency checking, scheduled calculations and reporting functions in tabular and graphical formats in a single Microsoft Excel®-based workbook package, automated using linked worksheets) should remain constant. For example, definitions of programs and units of analysis differ from country to country, but once clearly defined, TCAT can be modified for use in these settings [8, 9]. Thus, TCAT is a promising new costing tool that derives from established methodologies and reflects economic principles. In addition to its research applications, the potential for TCAT to be used in a self-administered manner opens up new possibilities for treatment programs to gain insight into their own costs and use economic information to support management decision making. Supporting researchers and practitioners in the collection and application of cost data is expected to help improve the quality of care [8, 9]. Thus, patients with gout have significant direct and indirect costs associated with their disease. The sodium monourate burden associated with gout leads to both increased disability and attacks that significantly affect health-related quality of life and physical function. Strategies are needed to improve patient outcomes while reducing the economic burden of gout

for managed care, employers and insurers. Identifiable areas where improvements can be made to reduce costs in our opinion are as follows:

- prescribing optimal treatments for the management of acute attacks, preventive treatment for recurrent attacks and initiating treatment to reverse hyperuricemia in patients with gout at an earlier stage of the disease than is usually done today;
- raising awareness of treatment adherence, as non-compliance is one of the causes of progression to chronic gout and therefore higher costs;
- updating the effective use of available long-term treatment strategies, such as allopurinol, is good. However, the development of new, highly selective therapies for the control of hyperuricemia, and attenuation of gouty inflammation are indicated for certain patient populations. These new therapies will be particularly useful for patients with extensive or advanced comorbidities, which often limit the effective use of traditional gout treatment;
- is a reasonable goal to increase the awareness of primary care physicians, who see the majority of gout patients, of the latest therapies and guidelines and to increase their skills in improving medication adherence in their patient populations. In this way, progression of gout to more severe and costly stages could be prevented or avoided.

GENERAL CONCLUSIONS

1. Gout is characterized by a marked and multiple associated comorbid background, which significantly increases with advancing age. There is a direct correlation between early onset of gout and the occurrence of comorbidities: the mean number of comorbidities is twice as high in patients with onset over 60 years of age, but at onset under 60 years of age the mean number of associative comorbidities is 4.5 [3.5; 5.6].
2. The evolution of the inflammatory process and disease progression determined that in patients with gout onset under 60 years of age the development of ischemic heart disease, chronic heart failure and nephrolithiasis occurs significantly earlier than in patients with onset over 60 years of age – 49.5±7.1 years and 58.8±4.8 years; 55.4±4.2 years and 66.1±8.7 years; 41.4±9.2 years and 53.8±13.4 years, respectively ($p < 0.05$ years). Thus, gout presents a significant causative factor for comorbidities.
3. The specific pathological change can be considered the onset of hypertension at an early age, which induces specific developmental changes associated with the early development of gout: the mean age of onset of hypertension in patients with the development of gout up to 60 years is significantly lower than in the general population (36.9±5.8 years) and demonstrates that young patients with hypertension belong to the risk group for gout.
4. The determinism of the factors causing the severe development of gout is combined with advancing age – in the elderly the chronicity of gouty arthritis appeared in a shorter time: at 103 (38.43%) of patients developed chronic arthritis within the first 5 years after the onset of gout ($\chi^2=6.915$, $df=1$, $p=0.0085$), while in 67 (28.75%) ($\chi^2=0.038$, $df=1$, $p=0.8458$) of middle-aged patients (under 60 years) chronic arthritis developed 5 years after the onset of gout.

5. With advancing age, the frequency of acquired causative factors for gout increases, and their correction would reduce the burden of the disease and its severity: low doses of Acetylsalicylic acid increase the progressive risk of gout by up to 37% (95% CI, 2.5%-18.1%), diuretics – by up to 46% (95% CI, 8.1%-22.4%), alcohol consumption – from 13% to 27% (95% CI, 9.1%-18.8%), hypertension – up to 77% (95% CI, 3.9%-21.1%), consumption of purine-saturated foods – from 55% to 69% (95% CI, 26.7%-38.9%), overweight and obesity – from 59% to 78% (95% CI, 8.1%-29.7%).
6. Determination of economic feasibility expressed by analysis of direct medical costs according to age and comorbidity, showed that in elderly patients with gout in hospital treatment, in 62.5% of cases the recommendations for the treatment of gout according to the European Anti-Rheumatic League (2016) are relatively followed, which reduces the effectiveness of health care and is responsible for the unreality of real costs, with the focus only on the underlying disease.
7. During just one year the frequency of hospitalizations of elderly patients (≥ 60 years) with gout is significantly higher (1.4 cases per year) compared to patients of working age (0.9 cases per year), which significantly affects the cost of health care, and the presence of comorbidities even more increases financial expenses, being in direct correlation with the severity and progressive degree of the underlying disease. Tackling the causative factors would make expenditure more efficient and combat the severe course of the disease by reducing the number of comorbidities.
8. The direct costs for the treatment of patients with gout associated with comorbid pathology (separately and jointly), according to the National Clinical Protocols corresponding to each separate nosology, increase significantly with the advancing age of the patients: the average cost per year of gout treatment in middle-aged patients was 26 073.85 LMD without and 142 754.94 LMD taking into account comorbid pathology, and in the elderly – 40 321.36 LMD and 297 003.50 LMD respectively. The costs per case treated in hospital for patients over 60 years of age with gout, calculated in various ways, differ significantly, determining the opportunity for further improvement and optimization.

Recommendations for the teaching process

1. Incorporating age-specific therapeutic and developmental differentiation for gout into the educational process.
2. Addressing comorbid factors:
 - a. incorporating in the study program the impact of cardiovascular pathology on gout development;
 - b. consider the comorbid renal issues and influence on the gout process;
 - c. examining the associations of osteoarticular pathologies in gout and identifying their evolutionary features.
3. Developing skills for managing elderly patients with gout and associated comorbidities.
4. Comprehensive analysis of the impact of various associated treatments on gout progression and strategies for optimizing combined therapy.

Practical recommendations

1. To update the National and Hospital Clinical Protocols for gout and its prevalent comorbidities, it's essential to develop management strategies and clinical guidelines tailored to various healthcare delivery levels. This includes protocols for primary care (family doctors), secondary care (district and municipal hospitals), and tertiary care (national hospitals), ensuring the development of appropriate management protocols for each level.
2. To include young patients (under 60 years of age) with early onset of hypertension and ischaemic heart disease in the risk group for the development of hyperuricaemia and gout. The earlier the onset of hypertension and chronic heart failure, the higher the risk of developing hyperuricaemia and gout.
3. To offer comprehensive support to non-profit medical organizations in creating patient guidelines, focusing on care provision for conditions related to gout, such as hyperuricemia, and associations between gout and metabolic syndrome.
4. Preventing gout in elderly patients should involve strategies to avoid the unnecessary prescription of diuretics and antiplatelet agents. Educational efforts should emphasize the impact of these medications on hyperuricemia across all levels of medical education, including medical students, residents, and continuous medical education for practicing physicians.
5. Enhance efforts to promote a healthy lifestyle among patients by engaging more patient-focused non-governmental organizations. Key focuses should include reducing and maintaining optimal body weight, lowering alcohol intake, and minimizing the consumption of excessive meat and seafood.
6. When rationalising the costs of treating gout, particularly in elderly patients, it is necessary to take into account the cost impact of comorbid pathology.
7. When calculating the cost of clinical and statistical groups of medical care cases for gout, it is necessary to consider the age of the patient.
8. The cost assessment for cases treated in inpatient care should take into account the association of comorbid diseases and the differentiation of gout complications. This approach aims to achieve efficient savings and adjust financial resources across various levels of specialized care.

SUGGESTIONS FOR FUTURE RESEARCH

Understanding and managing gout, has posed a significant challenge to the skilled physicians throughout the history of medicine. However, the field has seen substantial progress, evolving continuously and recently experiencing significant breakthroughs. Our deeper insight into the disease's pathogenesis, alongside more sophisticated diagnostic tools, has greatly improved. Most importantly, we now have access to a broader spectrum of therapeutic options, enhancing our ability to effectively manage the condition."

The future agenda in this area is likely to address the following issues:

1. Intensive studies in genomics and proteomics. These will help us to better understand the genetic predisposition of the disease and susceptibility to adverse drug effects. They will also provide potential therapeutic breakthroughs.
2. Investigating the possible role of the microbiome in gout concomitantly with its metabolic counterparts.
3. Efforts to standardize international medical practices for gout, including outcome measures, staging, and management.
4. Emphasis on patient and physician education. This would be an extremely cost-effective approach.

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADSS	Alcohol Drug Services Study
BMI	body mass index
CKD	chronic kidney disease
CHF	chronic heart failure
CRP	C-reactive protein
CI	confidence interval
DF	degree of freedom
EULAR	European League Against Rheumatism
GC	general costs
GFR	glomerular filtration rate
GHDx	Global Health Data Exchange
IHD	ischemic heart disease
IR	insulin resistance
IQR	interquartile range
HU	hyperuricemia
LMD	leu Moldova
MS	metabolic syndrome
NCP	National Clinical Protocols
NSAID	non-steroidal anti-inflammatory drugs
NHANES	National Health and Nutrition Examination Survey
NHIC	National Health Insurance Company
OA	osteoarthritis
PsA	psoriatic arthritis
p	coefficient of statistical significance according to the T-student criterion
SD	standard deviation
SDI	socio-demographic index
SMC	sodium monourate crystals
TCAT	treatment cost analysis tool
T2DM	type 2 diabetes mellitus
WHO	World Health Organization
%	number of patients in percent
χ^2	coefficient of agreement

ADNOTARE

Rotaru Larisa „Comorbidități în gută: studiul polimorfismului clinic, diagnosticului, strategiilor de tratament și prognostic”. Teză de doctor habilitat în științe medicale, Chișinău, 2024.

Structura tezei. Lucrarea a fost expusă pe 256 de pagini de text electronic și se compartimentează în: introducere, 5 capitole, discuții, 8 concluzii și 12 recomandări, indice bibliografic (240 de titluri), 36 de figuri, 45 de tabele, 13 anexe. Rezultatele cercetării au fost prezentate în 62 de publicații.

Cuvinte-cheie: acid uric, hiperuricemie, gută, boli metabolice, comorbidități, diagnostic, scorul de severitate.

Domeniul de studiu. Reumatologie

Scopul studiului. Evaluarea comorbidității pacienților de diferite vârste afectați de gută cu argumentarea clinică și economică privind îmbunătățirea managementului de evaluare clinico-paraclinică în acordarea asistenței medicale acestor pacienți.

Obiectivele studiului. 1. Evaluarea statutului comorbid la pacienții suferinzi de gută de diferite vârste.

2. Analiza evoluției procesului inflamator și a progresiei bolii la pacienții cu gută prin prisma diferitor decade ale vârstei. 3. Specificarea modificărilor patologice ale organelor interne și a particularităților evolutive ale afectărilor extraarticulare la pacienții cu gută. 4. Determinarea factorilor provocatori și a influenței lor asupra debutului, caracteristicilor și evoluției gutei la persoanele vârstnice. 5. Analiza posibilității corecției factorilor provocatori la pacienții vârstnici prin ajustarea tratamentului non-farmacologic și farmacologic.

6. Determinarea fezabilității economice exprimate prin analiza costurilor medicale directe în funcție de vârstă și comorbiditate, cu elaborarea principiilor de eficientizare a cheltuielilor. 7. Analiza economică a costurilor unui caz tratat staționar, cu elaborarea principiilor de eficientizare a cheltuielilor în funcție de evoluție.

8. Elaborarea recomandărilor pentru eficientizarea managementului clinic și fezabilității economice de acordare a asistenței medicale pacienților vârstnici cu gută.

Noutatea și originalitatea științifică. În cadrul unui studiu observațional, descriptiv, transversal, pacienții cu gută au fost cercetați multidimensional. Au fost evaluate factorii provocatori, debutul și evoluția, frecvența comorbidităților la pacienții vârstnici cu gută în comparație cu indicatorii similari ai pacienților din alte grupuri de vârstă. A fost efectuată o evaluare a conformității „practicii tipice” de gestionare a pacienților vârstnici cu gută într-un cadru spitalicesc, ținând cont de recomandările internaționale valabile pentru perioada studiului. S-a demonstrat importanța factorilor controlabili dobândiți care afectează severitatea gutei la pacienții vârstnici, dintre care: administrarea diureticelor și dozelor mici de Acid acetilsalicilic, obezitatea, respectarea dietei și consumul excesiv de alcool. S-au analizat recomandările pentru îmbunătățirea metodologiei de analiză clinică și economică a costurilor de acordare a asistenței medicale pacienților vârstnici cu gută, luând în considerare corectarea contextului comorbid, acestea fiind fundamentate și testate științific.

Problema științifică importantă soluționată în teză. Pe baza analizei factorilor provocatori care cauzează guta la vârstnici, au fost identificate principalele metode de abordare optimă a prevenirii și tratamentului acesteia, care includ medicamente (diuretice, Acid acetilsalicilic), nerespectarea regimului alimentar, consumul de alcool și prezența sindromului metabolic. În baza datelor obținute, a fost determinat rolul semnificativ al comorbidităților în formarea costurilor pentru furnizarea de asistență medicală pacienților vârstnici cu gută. În special, prezența HTA, CPI, BCR crește semnificativ aceste costuri. Sunt prezentate recomandări metodice pentru optimizarea metodologiei de modelare a costurilor de acordare a îngrijirilor medicale unui pacient vârstnic cu gută, ținând cont de comorbidități, care includ revizuirea numărului de examinări, atât de laborator, cât și instrumentale, pentru fiecare boală comorbidă.

Semnificația teoretică. Datele epidemiologice obținute privind distribuția frecvenței factorilor provocatori de gută la pacienții vârstnici vor permite stratificarea determinată științific a riscurilor la anumiți pacienți și vor fi utilizate în mod activ la crearea recomandărilor pentru prevenirea și tratamentul bolii. Caracteristicile debutului și ale evoluției gutei la pacienții vârstnici identificați pe parcursul studiului în comparație cu pacienții de vârstă medie vor optimiza desfășurarea măsurilor diagnostice și terapeutice la pacienții din acest grup de vârstă.

Valoarea aplicativă. Analizându-se factorii provocatori pentru dezvoltarea gutei la vârstnici, au fost identificate principalele cauze care afectează lipsa unei abordări optime a prevenirii și tratamentului acesteia. În baza datelor obținute, a fost determinat un rol semnificativ al patologiei comorbide în formarea costurilor pentru furnizarea de asistență medicală pacienților vârstnici cu gută. Sunt prezentate recomandări metodice pentru optimizarea metodologiei de modelare a costurilor de acordare a îngrijirilor medicale unui pacient vârstnic cu gută, ținând cont de patologia concomitentă.

Implementarea rezultatelor. Rezultatele studiului au fost incluse în Protocolul Clinic Național „Guta la adult”, se aplică în procesul didactic al Departamentului Medicină Internă, în practica Disciplinei de reumatologie și nefrologie a IP USMF „Nicolae Testemițanu” și în secția de Artrologie a IMSP SCR „Timofei Moșneaga”.

SUMMARY

Rotaru Larisa: „*Gout comorbidities: the study of clinical polymorphism, diagnosis, treatment strategy and prognosis*”. PhD thesis habilitated in Medical Sciences, Chisinau, 2024.

Thesis structure. The work was exposed on 256 pages of electronic text and is divided into: introduction, 5 chapters, discussions, 8 conclusions and 12 recommendations, bibliographic index (240 titles), 36 figures, 45 tables, 13 annexes. The results of the research were presented in 62 publications.

Keywords: uric acid, hyperuricemia, gout, metabolic diseases, comorbidities, diagnosis, severity score.

Domain of research. Rheumatology

Aim of the study. Assessment of the comorbidity of patients of different ages affected by gout with clinical and economic rationale for improving the management of clinical-paraclinical assessment in providing care to these patients.

Study objectives. 1. Assessment of comorbid status in gout patients of different ages. 2. Analysis of the evolution of the inflammatory process and disease progression in patients with gout in the different decades of age. 3. Specify the pathological changes of internal organ pathology and the evolutionary peculiarities of extra-articular damage in patients with gout. 4. Determine the triggering factors and their influence on the onset, characteristics and evolution of gout in the elderly. 5. Analysis of the possibility of correcting modifiable risk factors in elderly patients by adjusting non-pharmacological and pharmacological treatment. 6. Determination of economic feasibility expressed by analysis of direct medical costs according to age and comorbidity, with elaboration of principles of cost efficiency. 7. Economic cost analysis of an inpatient case, with development of cost efficiency principles according to evolution. 8. Development of recommendations for streamlining clinical management and economic feasibility of providing care to elderly patients with gout.

Scientific novelty and originality. In an observational, descriptive, cross-sectional study, patients with gout were investigated multidimensionally. Challenging factors, onset and progression, frequency of comorbidities in elderly patients with gout were assessed in comparison with similar indicators of patients in other age groups. An assessment of the compliance of the „typical practice” management of elderly patients with gout in a hospital setting was performed, taking into account the international guidelines valid for the study period. The importance of acquired controllable factors affecting the severity of gout in elderly patients was demonstrated, including: the administration of diuretics and low doses of Acetylsalicylic acid, obesity, dietary compliance and excessive alcohol consumption. Recommendations for improving the methodology of clinical and economic cost analysis of healthcare delivery for elderly patients with gout, taking into account the correction of the comorbid context, have been reviewed and are scientifically substantiated and tested.

The scientific problem solved in the thesis. Based on the analysis of the factors that cause gout in the elderly, the main methods of optimal approach to its prevention and treatment have been identified, which include drugs (diuretics, Acetylsalicylic acid), dietary non-compliance, alcohol consumption and the presence of metabolic syndrome. Based on the data obtained, the significant role of comorbidities in shaping the costs of providing care to elderly patients with gout was determined. In particular, the presence of ischemic heart disease, chronic heart failure, chronic renal failure significantly increases these costs. Methodological recommendations are presented for optimizing the methodology for modeling the costs of providing health care to an elderly patient with gout, taking into account comorbidities, which include reviewing the number of examinations, both laboratory and instrumental, for each comorbid disease.

Theoretical significance. The epidemiological splints obtained on the distribution of the frequency of gout risk factors in elderly patients will allow scientifically determined stratification of risks in certain patients and will be actively used to create recommendations for the prevention and treatment of the disease. The characteristics of the onset and development of gout in elderly patients identified during the study compared to middle-aged patients will optimize the conduct of diagnostic and therapeutic measures in patients in this age group.

Applicative value of the study. When analyzing the factors that cause the development of gout in elderly, the main causes affecting the lack of an optimal approach to its prevention and treatment have been identified. Based on the data obtained, a significant role of comorbid pathology in the formation of costs for the provision of medical care to elderly patients with gout was determined. Methodical recommendations are presented for optimizing the methodology for modeling the costs of providing medical care to an elderly patient with gout, taking into account the concomitant pathology.

Results implementation. The results of the study were included in the National Clinical Protocol „Gout in adult”, is applied in the didactic process of the Department of Internal Medicine, in the practice Department of Rheumatology and Nephrology of *Nicolae Testemitanu* SMPHU and in the Clinical Department of Arthrology of *Timofei Moşneaga* Republican Clinical Hospital.

РЕЗЮМЕ

Ротару Лариса: „Сопутствующие заболевания при подагре: изучение клинического полиморфизма, диагностика, стратегии лечения и прогноз”. **Диссертация на соискание степени доктора хабилитат медицинских наук, Кишинэу, 2024.**

Структура диссертации. Работа представлена на 256 страницах электронного текста и состоит из: введения, 5 глав, обсуждение, 8 выводов, 12 практических рекомендаций, библиографии (240 источника), 36 рисунков, 45 таблиц, 13 приложений. Результаты исследования были опубликованы в 62 научных работах.

Ключевые слова: мочевая кислота, гиперурикемия, подагра, метаболические заболевания, сопутствующие заболевания, диагностика, оценка тяжести.

Цель исследования. Оценка коморбидности пациентов разного возраста, страдающих подагрой, с клинико-экономическим обоснованием для улучшения управления клинико-параclinical оценкой при оказании помощи этим пациентам.

Задачи исследования. 1. Оценка коморбидного статуса у больных подагрой разного возраста. 2. Анализ эволюции воспалительного процесса и прогрессирования заболевания у пациентов с подагрой в разных возрастных категориях. 3. Уточнить патологические изменения внутренних органов и эволюционные особенности внесуставного поражения у больных подагрой. 4. Определить провоцирующие факторы и их влияние на возникновение, характеристики и эволюцию подагры у пожилых людей. 5. Анализ возможности коррекции модифицируемых факторов риска у пациентов пожилого возраста путем корректировки нефармакологического и фармакологического лечения. 6. Определение экономической целесообразности, выраженной в анализе прямых медицинских затрат в зависимости от возраста и коморбидности, с разработкой принципов экономической эффективности. 7. Анализ экономических затрат на стационарный случай с разработкой принципов эффективности затрат в зависимости от эволюции. 8. Разработка рекомендаций по оптимизации клинического менеджмента и экономической целесообразности оказания помощи пожилым пациентам с подагрой.

Научная новизна. В обсервационном, описательном, перекрестном исследовании пациентов с подагрой были комплексно обследованы. Были оценены провоцирующие факторы, дебют и эволюция заболевания, частота сопутствующих заболеваний у пожилых пациентов с подагрой в сравнении с аналогичными показателями пациентов других возрастных групп. Проведена оценка соответствия „типичной практики” ведения пожилых пациентов с подагрой в условиях стационара с учетом международных рекомендаций, действующих на период исследования. Показана важность приобретенных контролируемых факторов, влияющих на тяжесть подагры у пожилых пациентов, в том числе: прием диуретиков и низких доз ацетилсалициловой кислоты, ожирение, соблюдение диеты и чрезмерное употребление алкоголя. Рассмотрены и научно обоснованы рекомендации по совершенствованию методологии анализа клинико-экономических затрат на оказание медицинской помощи пожилым пациентам с подагрой с учетом коррекции сопутствующих заболеваний.

Важность решенной научной проблемы. На основе анализа факторов, вызывающих подагру у пожилых, определены основные методы оптимального подхода к ее профилактике и лечению, к которым относятся лекарственные препараты (диуретики, ацетилсалициловая кислота), несоблюдение диеты, употребление алкоголя и наличие метаболического синдрома. На основании полученных данных, была определена значительная роль сопутствующих заболеваний в формировании затрат на оказание помощи пожилым пациентам с подагрой. В частности, наличие ишемической болезни сердца, хронической сердечной недостаточности, хронической почечной недостаточности значительно увеличивает эти затраты. Представлены методические рекомендации по оптимизации методики моделирования затрат на оказание медицинской помощи пожилому пациенту с подагрой с учетом сопутствующих заболеваний, которые включают пересмотр количества обследований по каждому сопутствующему заболеванию.

Теоретическая значимость. Полученные эпидемиологические данные по распределению частоты провоцирующих факторов при подагре у пациентов пожилого возраста позволили определить стратификацию рисков у отдельных пациентов и были использованы для создания рекомендаций по профилактике и лечению заболевания. Выявленные в ходе исследования особенности возникновения и развития подагры у пациентов пожилого возраста по сравнению с пациентами среднего возраста позволили оптимизировать проведение диагностических и лечебных мероприятий у пациентов этой возрастной группы.

Прикладная значимость. При анализе провоцирующих факторов развития подагры в пожилом возрасте выявлены основные причины, влияющие на отсутствие оптимального подхода к ее профилактике и лечению. На основании полученных данных определена значительная роль сопутствующей патологии в формировании затрат на оказание медицинской помощи пожилым пациентам с подагрой. Представлены методические рекомендации по оптимизации методики моделирования затрат на оказание медицинской помощи пожилому пациенту с подагрой с учетом сопутствующей патологии.

Внедрение в практику. Результаты исследования были включены в Национальный Клинический Протокол „Подагра у взрослых”, были внедрены в дидактический процесс и в клиническую практику Дисциплины ревматологии и нефрологии, Департамента Внутренних Болезней, ГУМиФ „Николае Тестемичану” и в отделении Артрологии Республиканской Клинической Больницы „Тимофей Мошняга”.

ROTARU LARISA

**COMORBIDITIES IN GOUT: STUDY OF CLINICAL POLYMORPHISM, DIAGNOSIS,
TREATMENT STRATEGIES AND PROGNOSIS**

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