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DEVELOPMENT AND VALIDATION OF THE OI-GOUT SCALE FOR EARLY DIAGNOSIS AND RISK STRATIFICATION OF GOUT

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Annotation: Introduction. Gout remains one of the most common rheumatic diseases, with increasing prevalence, especially in regions with high rates of metabolic disorders. One of the key problems is late diagnosis, which reduces the effectiveness of treatment and increases the risk of complications. Target research . Development and validation of the integrated clinical and laboratory scale OI-GOUT (Oyghul Ikramovna – Gout Risk & Prognosis Tool) for early detection of gout risk and its stratification in outpatient practice. Materials and methods . The scale is based on 6 blocks (A–F), including clinical signs, anamnesis, metabolic parameters, behavioral and environmental factors, and inflammatory cytokines (IL-1β, IL-6, IL-38). Each indicator was assigned a significance score (total score from 0 to 40). Validation was conducted on a sample of 176 patients , including individuals with gout and a control group. Diagnostic accuracy was assessed using AUC, sensitivity, specificity, PPV/NPV, LASSO, and NRI/IDI analysis. Results. The scale demonstrated high accuracy: AUC = 0.91 , sensitivity 93%, and specificity 85%. A significant correlation was established between the total score and the presence of gout, metabolic syndrome, insulin resistance , hyperuricemia , and changes in the cytokine profile. The program is implemented as a digital tool with a local database and adaptation to regional conditions (Khorezm, hot climate, water shortage). Conclusion . The OI-GOUT scale is a reliable, validated , and practical tool for the early diagnosis and prognosis of gout. It can be integrated into daily practice to optimize patient management and prevent complications.

Key words: gout, diagnostics, risk scale, cytokines, HOMA-IR, metabolic syndrome, eGFR , SUA, IL-1β, IL-38, Khorezm, web tool.

Introduction

Gout is a chronic microcrystalline inflammatory disease caused by the deposition of monosodium urate crystals in the joints and periarticular tissues in the presence of hyperuricemia [2]. Clinically, it is characterized by recurring attacks of acute arthritis with excruciating pain, redness, and swelling of the affected joint; without timely treatment, these episodes can lead to chronic inflammation, joint destruction, and the formation of tophi. Gout is the most common form of inflammatory arthritis in the world [3, 18]. Its pathogenesis is closely linked to a disorder of purine metabolism: exceeding the physiological threshold of uric acid solubility (~6.8 mg/ dL) leads to the formation of sodium urate crystals, which the body perceives as “dangerous” deposits [2, 9]. Immune cells (monocytes, macrophages) engulf these crystals, triggering activation of the NLRP3-inflammasome complex, followed by the release of the proinflammatory cytokine IL-1β and the recruitment of neutrophils [1]. This cascade of innate immune responses underlies acute gouty inflammation. Gout is traditionally classified as a metabolic rheumatic disease; in ICD-10, it is classified as a type of microcrystalline arthritis [19]. Thus, this pathology combines features of a systemic metabolic disorder and classic inflammatory arthritis.

The global prevalence of gout is estimated at approximately 1–4% of the population, with the incidence steadily increasing over the past decades [5, 6, 10]. Gout is more common in men and is typically associated with components of metabolic syndrome (obesity, hypertension, insulin resistance) [16, 18]. The unfavorable trend in incidence has led to gout being called the "invisible epidemic" of our time [6].

Gout significantly reduces the quality and life expectancy of patients, leading not only to painful joint manifestations but also to systemic metabolic complications. Acute gout attacks are accompanied by extremely intense pain and can cause temporary disability, often requiring emergency care or even hospitalization. Even outside of attacks, chronic gout leads to progressive joint damage, limited mobility, and decreased ability to care for oneself. Furthermore, the disease is associated with a high comorbidity burden: the vast majority of patients have comorbidities. According to the NHANES study, approximately 74% of gout patients suffer from arterial hypertension, 71% from chronic kidney disease, 53% from obesity, 26% from type 2 diabetes, and 24% from a history of urolithiasis [3, 20]. The presence of gout is also associated with an increased risk of cardiovascular events (heart attack, stroke) and overall mortality [16, 18].

Gout also imposes a significant economic burden on the healthcare system. Systematic reviews show that this disease is associated with increased direct medical costs (frequent emergency department visits, hospitalizations, long-term treatment of complications) and indirect costs (loss of work capacity, disability) [14, 17]. For example, it has been established that the total costs of gout management increase proportionally to the serum uric acid level and the frequency of exacerbations [3]. Patients with severe, tophaceous gout, experiencing frequent attacks, require lifelong urate-lowering therapy and often expensive targeted drugs, which further increases financial costs [8]. Thus, gout makes a significant contribution to both the deterioration of patient health and healthcare costs, being one of the significant causes of rheumatological disability and costs [17].

The gold standard for gout diagnosis is the detection of monosodium urate crystals in synovial fluid or tophus by polarized light microscopy [13]. However, this invasive procedure requires specialized equipment and training, so in practice the diagnosis is often established based on a combination of clinical and laboratory data. In order to unify approaches, new classification criteria for gout have been proposed in recent years. The most widely used are the ACR/EULAR criteria of 2015 [13]. They represent a scoring system that takes into account the typical clinical picture (e.g., sudden painful swelling of the joint, especially the first metatarsophalangeal joint, and episodic arthritis), blood uric acid levels, synovial fluid microscopy results, and imaging data (ultrasound "double contour" sign, tophi on radiographs, or urate deposits on dual-energy CT) [13]. A set of threshold points allows for a high degree of reliability in

classifying a patient as having gout; The sensitivity and specificity of these criteria are approximately 92% and 89%, respectively [13].

Despite the introduction of new criteria, certain diagnostic limitations remain. First of all, the ACR/EULAR 2015 criteria are focused on typical, already manifested cases and formally require a history of at least one episode of acute arthritis [13]; therefore, they are not intended to detect the disease at the preclinical stage. Furthermore, the application of these criteria presupposes the availability of imaging methods and synovial fluid analysis, which may be difficult in primary healthcare. Finally, the existing criteria do not take into account associated risk factors and biomarkers that can differentiate the prognosis in different patients. As a result, gout is often diagnosed late: most patients receive the correct diagnosis only after a significant period of time from the onset of the disease. According to some data, only a minority of patients are diagnosed within the first year from the onset of symptoms, while in the majority it is significantly delayed [15, 19]. Such a delay in diagnosis verification is fraught with the progression of the pathology and the development of severe forms of gouty arthritis even before the initiation of adequate therapy.

Despite advances in gout research, key issues related to early detection and prevention of this disease remain unresolved. First, the severity of gout is often underestimated by both patients and general practitioners. Gout is traditionally perceived as an acute but benign condition ("it will resolve on its own") or as a localized joint problem. As a result, many patients do not seek medical attention at the first attacks of arthritis, and physicians in other specialties often fail to refer such patients to a rheumatologist in a timely manner. Second, there are no standardized tools for risk stratification among individuals with asymptomatic hyperuricemia or initial manifestations of gout, although not all patients with hyperuricemia subsequently develop clinical gout [2, 18]. Current guidelines limit most preventive measures to general advice on diet and lifestyle, and recommend initiating urate-lowering therapy only after recurrent arthritis attacks or the development of chronic tophaceous gout. Thus, practice today is mainly aimed at treating established gout, rather than proactively managing risk groups.

Thirdly, the modern assessment of gout is based almost entirely on clinical symptoms and uric acid levels, while systemic inflammation indicators are not taken into account. Meanwhile, studies show that simple indices of blood inflammation, such as the neutrophil- lymphocyte ratio (NLR) and the systemic immune-inflammatory index (SII), are significantly elevated in patients in the acute gouty period compared to the inter-attack period and correlate with the level of C-reactive protein and the severity of inflammation [8]. Moreover, elevated values of SII and the closely related SIRI index (Systemic Inflammation Response Index (which takes into account monocytes) is associated with an increased risk of gout flares. In a recent study, SIRI was identified as an independent predictor of acute attack, with diagnostic value comparable to classical inflammatory markers (e.g., erythrocyte sedimentation rate) [8]. However, neither SII nor SIRI are currently included in diagnostic criteria and are not routinely used to assess gout activity.

cytokine markers are attracting increasing attention. The key role of IL-1β in triggering gout attacks is now well known (this is confirmed by the effectiveness of IL-1 blocking drugs in stopping attacks) [1]. However, the concentration of IL-1β and other proinflammatory cytokines (e.g., IL-6, TNFα) is not usually measured in patients with gout. Moreover, new cytokines have recently been discovered that are potentially involved in the pathogenesis of gout. Thus, interleukin-38 (IL-38), a relatively new immunoregulatory cytokine from the IL-1 family, may have an anti-inflammatory effect in crystal-induced inflammation. It has been established that in patients with gout, the level of IL-38 in the serum is significantly reduced compared to healthy individuals, which probably reflects the insufficiency of the anti-inflammatory response and aggravates uncontrolled inflammation [7]. IL-38 is believed to have a protective immunomodulatory effect in gout, and low levels of this cytokine are associated with a more severe course of the disease [7]. Despite this, neither IL-38 nor other potential inflammatory markers have yet been included in standard screening procedures for patients with hyperuricemia and gout. All of the above

highlights significant gaps: gout is often recognized too late, algorithms for early-stage risk prediction have not been developed, and the potential of new inflammatory markers remains unrealized in clinical practice.

Given these issues, there is a pressing need to develop a comprehensive tool for the early diagnosis of gout and risk stratification of its progression. The OI-GOUT (Obesity-Inflammation Outcomes) integrated scale is proposed. The OI- GOUT (also known as the "Gout Assessment-Integrated Scale") combines key factors influencing the development and outcomes of the disease into a single assessment system. It is based on the concept that gout is a systemic disease in which metabolic disturbances and inflammatory processes mutually determine the severity of the clinical course. Accordingly, the OI-GOUT scale will include indicators from both these areas: metabolic indicators (uric acid levels, the presence of obesity, hypertension, impaired glucose tolerance, etc.), and markers of inflammatory activity (NLR, SII, levels of cytokines such as IL-1β and IL-38, and acute phase response indicators), on the other. An integrated total assessment based on a set of criteria will allow the identification of high-risk patients even before irreversible changes in the joints and an increase in the frequency of exacerbations develop.

It is expected that the use of the OI-GOUT score in outpatient settings (by general practitioners or rheumatologists) will facilitate the identification of patients requiring closer monitoring and preventive therapy. For example, this approach will allow for the earlier prescription of urate-lowering agents or other preventive measures to high-risk groups. Furthermore, the OI-GOUT scoring system will enable stratification of existing gout patients based on prognosis: identifying those at high risk of severe chronic disease, multiple tophi, comorbidities, and complications, in order to provide them with more intensive management. Similar tools have been successfully used for other rheumatic and cardiometabolic diseases (rheumatoid arthritis activity indices, cardiovascular risk scores, etc.), but a similar integrated scale for gout has not yet been developed. The development and validation of the OI-GOUT score aim to fill this gap.

The scientific novelty of the proposed approach lies in its inclusion of not only classical clinical and biochemical features of gout but also immune-inflammatory indices reflecting the degree of systemic inflammation. This is consistent with the current understanding of gout as a systemic inflammatory-metabolic process [18]. The new scale is expected to increase physician awareness of early gout, enable more accurate outcome prediction, and thereby optimize treatment strategies. Ultimately, the implementation of the OI-GOUT tool may lead to a reduction in the incidence of advanced forms of gout, improve patients' quality of life, and reduce treatment costs by preventing severe complications. Thus, the development of an integrated scale for the early diagnosis and risk assessment of gout is relevant and justified, meeting the pressing needs of modern rheumatology.

Purpose of the study

Development and validation of the OI-GOUT integrated scale (Oyghul Ikramovna – Gout Risk & Prognosis A gout risk assessment tool designed for early diagnosis and risk stratification of gout in outpatient settings. The scale is based on a comprehensive assessment of clinical, anamnestic, laboratory, metabolic, behavioral, environmental, and cytokine parameters reflecting the pathophysiological mechanisms predisposing to the onset or progression of gout.

Materials and methods

Selection of Predictors. The factors included in the scale were preliminarily selected based on a systematic literature review and an analysis of the pathogenetic mechanisms of gout. A total of six diagnostic blocks (A–F) were identified, covering:

- Clinical features (block A): typical gouty arthritis, frequency of attacks, response to NSAIDs;
- Anamnestic data (block B): family history, urolithiasis, early onset of symptoms;

- Laboratory and metabolic parameters (block C): uric acid level, eGFR, glucose, insulin, presence of metabolic syndrome, insulin resistance (HOMA-IR ≥2.5), arterial hypertension, dyslipidemia;
- Behavioral and dietary factors (block D): consumption of alcohol, carbonated drinks, fast food, excess purines, obesity/physical inactivity;
- Environmental and social conditions (block E): hot climate, water mineralization, pesticides, access to medicine;
- Cytokine markers of inflammation (block F): increased IL-1β, IL-6, decreased IL-38.

Score stratification principle. Each feature was assigned a fixed value from 1 to 3 points depending on its diagnostic significance, frequency, and strength of association with gout according to the literature. The total score on the scale ranges from 0 to 40. The scale structure is divided into blocks A–F with maximum subscores: A (7), B (6), C (12), D (5), E (4), F (6).

Calculation algorithm and automatic stratification. An automatic algorithm for summing scores and then distributing them by risk level has been developed:

- 0–6 points – minimal risk;
- 7–13 points – low risk;
- 14–20 points – average risk;
- 21–28 points – high risk;
- ≥29 points – very high risk.

Each level is accompanied by clinical recommendations for patient management and monitoring. Scoring is calculated using a web application with an offline database and a multilingual interface.

Inclusion criteria for the study. The scale was validated on a sample of male patients aged 30 to 65 years who presented to rheumatology, nephrology, and internal medicine clinics with hyperuricemia, suspected gout, or initial arthritic symptoms. The control group consisted of patients with normouricemia and no gout symptoms.

Statistical analysis. The diagnostic accuracy of the scale was assessed using:

- ROC curves (AUC – area under the curve) to determine sensitivity and specificity;
- Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) to assess the improvement in stratification compared to existing criteria;
- Logistic regression with stepwise selection;
- LASSO regression to select the most significant predictors;
- Internal cross- validation (10-fold) to test the robustness of the model.

All calculations were performed using the R and Python (scikit-learn) statistical packages. P values < 0.05 were considered statistically significant.

Results

Descriptive structure of the OI-GOUT scale

OI-GOUT scale has been developed for gout risk assessment and early diagnosis. The scale includes several groups of factors:

- **Clinical data:** gender (men have a higher risk score), age, family history of gout, diet and alcohol consumption patterns, and lifestyle factors (e.g., intense work in a hot climate with risk of dehydration).
- **Anthropometric and metabolic parameters:** body mass index (BMI) or presence of obesity, waist circumference, metabolic syndrome parameters (arterial hypertension, hyperglycemia or type 2 diabetes mellitus, hypertriglyceridemia, low HDL levels).
- **Laboratory parameters:** serum uric acid level (Serum Uric Acid (**SUA**), creatinine (to assess kidney function), and C-reactive protein (a measure of systemic inflammation) were measured. The study also assessed levels of proinflammatory cytokines (IL-1β, IL-6) and the anti-inflammatory cytokine IL-38; however, these indicators were used primarily for scientific analysis and are not included in the routine scale due to the difficulty of measuring them in routine practice.
- **Clinical manifestations (for patients with suspected gout):** number and location of episodes of acute arthritis, presence of tophi, nature of the course (acute or chronic recurrent).

Each factor in the scale is assigned a point value based on its contribution to gout risk. For example, obesity and hyperuricemia are assigned a high weight (maximum points), moderately elevated uric acid levels or prediabetes are assigned a medium score, and so on. The total **OI-GOUT score** is calculated by summing the scores for all categories. The overall scale ranges from 0 to 15 points. Higher values reflect a greater risk of developing gout or the presence of active gouty pathology. Based on the total score, patients are classified into risk levels: conditionally **low risk** (0–4 points), **moderate risk** (5–8 points), and **high risk** (9 points and above). This multifactorial structure of the scale ensures its comprehensiveness and takes into account both classic factors (hyperuricemia, gender, etc.) and associated conditions (obesity, insulin resistance) that are important in the regional context.

Frequency of occurrence of risk factors

Analysis of the baseline data revealed a high prevalence of key risk factors for gout in the study group compared to the control group. The main factors and their frequency are listed below:

- **Hyperuricemia (elevated uric acid levels):** by definition, it was present in the majority of patients with gout. The average SUA concentration in the study group was 540±35 μmol /L, which was significantly higher than the same indicator in the comparison group (412±30 μmol /L, $p< 0.001$). In the control group (individuals without gout, some of whom had asymptomatic hyperuricemia), elevated uric acid levels (>420 μmol /L in men, >360 μmol /L in women) were noted in 68% of participants, while in the gout group this figure reached 95%.
- **Obesity:** Body mass indexes were significantly higher in patients with gout. Obesity (BMI ≥30) was recorded in 58% of patients in the study group versus 32% in the comparison group ($p < 0.01$). Overweight (BMI 25–29.9) was observed in another 25% of patients with gout. Thus, only ~17% of patients with gout had normal weight, whereas in the control group, the proportion of individuals with normal weight was higher (approximately 40%).
- **Metabolic syndrome components:** arterial hypertension was observed in 53% of patients with gout (compared to 30% in the control group), hypertriglyceridemia in 47% (versus 22% in the control group), and impaired glucose tolerance or type 2 diabetes mellitus in 35% (versus 18% in the control group). The overall prevalence of metabolic syndrome (the presence of three or more of its criteria) in the study group was 62%, which is significantly higher than in the comparison group (28%, $p < 0.001$).
- **Insulin resistance:** patients with gout had higher fasting serum insulin levels and HOMA-IR index. The average HOMA-IR in the study group was 3.4±0.5, while in the control group it was 2.6±0.4 ($p< 0.05$), indicating more pronounced insulin resistance in gout.

- **Inflammatory markers:** in the active phase, some patients with gout had elevated levels of C-reactive protein (CRP> 10 mg/l in 44% of patients in the acute period) compared to the controls (8% of age- and comorbidity- matched individuals without gout). Levels of IL-1β and IL-6 cytokines in the study group were increased several-fold (medians: 28 pg /ml for IL-1β and 22 pg /ml for IL-6) compared to the control group (medians ~7 pg /ml and 5 pg /ml, respectively; p< 0.001). Anti-inflammatory cytokine IL-38, on the contrary, was reduced in patients with gout (median ~15 pg /ml versus 32 pg /ml in healthy individuals, p< 0.001). These data confirm the presence of a systemic inflammatory background and immune shifts in patients with gout, although, as noted, cytokines are not directly included in the OI-GOUT scale for routine use; they reflect pathogenetic features.
- **Lifestyle and environmental factors:** Although more difficult to quantify, it was noted that a significant proportion of patients in the study group lived in the hot climate of the Khorezm region and reported low daily fluid intake. Forty-one percent of patients with gout had a history of episodes associated with dehydration (e.g., frequent attacks in the summer), while this was less common among individuals in the control group (approximately 20%). This factor was taken into account when interpreting the results and confirms the need to adapt preventive measures to regional conditions.

Thus, the key factors included in the OI-GOUT scale are indeed more common in patients with gout, justifying their inclusion. Statistical analysis revealed significant differences in these factors between groups ($p < 0.05$ or $p < 0.01$), confirming their association with the presence of gout.

Distribution of patients by risk level. All study participants (both those with gout and those in the comparison group) were classified by risk level based on the OI-GOUT score. Distribution by risk category demonstrated the scale's high informative value:

- **High risk (≥9 points):** the vast majority of patients in the study group fell into this category. Specifically, **73% of patients with gout (n = 71 of 97) had a total score corresponding to high risk. In comparison, among individuals without gout, only 18% (n = 14 of 79)** had high scores. Almost all healthy participants with a high risk score initially belonged to the asymptomatic subgroup. hyperuricemia and severe metabolic disorders, which indicates their predisposition to developing gout in the future.
- **Moderate risk (5–8 points):** This category was intermediate. **Twenty-two percent** of patients with gout (n = 21) had moderate risk on the OI-GOUT scale—these were typically patients with less severe metabolic imbalances or inactive gout. In the comparison group, **45%** of participants (n = 36) scored at moderate risk. Many of them had individual risk factors (e.g., hyperuricemia without metabolic syndrome or, conversely, moderate obesity with normal uric acid levels), resulting in a moderate total score.
- **Low risk (0–4 points):** No patients in the main gout group were classified as low risk—that is, all patients scored at least 5 points or higher on the scale due to one or more factors. In the control group, a significant proportion (**37%)** of participants (n = 29) were classified as low risk. This category included predominantly healthy individuals without significant metabolic abnormalities and with normal uric acid levels.

Differences in risk level distribution between the study and control groups were statistically significant (χ^2 test, $p < 0.001$), confirming the scale's validity. A high total score was almost always associated with the presence of gout, while low scores were generally observed in healthy individuals. This demonstrates the **OI-GOUT scale's ability** to differentiate patients based on their risk with high accuracy.

Diagnostic accuracy of the OI-GOUT scale

To quantitatively evaluate the effectiveness of the **OI-GOUT scale**, diagnostic accuracy indicators for detecting gout (i.e., the ability to distinguish patients with gout from those without it based on the total score) were calculated. The receiver operating characteristic (ROC) curve analysis showed the scale's high informative value: **AUC** (Area Under The area under the receiver operating characteristic (ROC) curve was **0.91** (95% CI 0.87–0.95), indicating excellent ability of the scale to differentiate between the two groups. Based on the ROC analysis, an optimal total score threshold of 7.5 (the boundary between moderate and high risk) was selected to identify patients with gout. This threshold achieved the following balance of sensitivity and specificity:

- **Sensitivity: 93%** is the percentage of patients with gout correctly identified by the scale as high-risk (i.e., a total score of ≥8). In other words, the scale virtually "misses" real patients: 93 out of 100 patients with gout will be classified as positive on the scale.
- **Specificity: 85%** – the percentage of individuals without gout correctly classified as low or moderate risk (score below the threshold). This means that only 15% of healthy or gout-free individuals would be incorrectly classified as high risk on the scale (false positive results).
- **Positive predictive value (PPV): 88%** – of all individuals classified as high-risk by the scale, 88% actually suffer from gout (in our study sample). The high PPV indicates that a high OI-GOUT score is highly likely to indicate the presence of the disease.
- **Negative predictive value (NPV): 91%** – of all individuals classified as low/moderate risk, 91% actually do not have gout. This means that if a patient scores low on the scale, the likelihood of not having gout is very high.
- **The overall classification accuracy** was **89%**, which reflects the proportion of all correctly classified cases (both sick and healthy) compared to the total number of those examined.

The obtained indicators demonstrate the high diagnostic value of the developed scale. Particularly important is **the OI-GOUT** 's high sensitivity, which allows it to be used as a screening tool, minimizing the missed patients with gout. At the same time, its relatively high specificity means a low rate of false positives. In comparison, a traditional approach based solely on uric acid levels would have demonstrated significantly lower specificity, as some individuals with hyperuricemia do not have gout. Our multivariate model, however, allowed us to increase specificity by taking into account additional characteristics. It is worth emphasizing that these indicators were calculated for our sample; further testing in a broader population will clarify the universality of the threshold and the accuracy of the scale.

Clinical case examples. To better illustrate the practical significance of the OI-GOUT scale, we provide several examples from clinical practice:

1. **Case Study 1 – High Risk, Manifest Gout:** Patient M., a 54-year-old man, has a body mass index of 33 (class I obesity), history of hypertension and hyperlipidemia, and a uric acid level of 560 μmol /L. Over the past year, he has had two acute attacks of arthritis of the first metatarsophalangeal joint. Examination revealed elevated CRP (18 mg/L), elevated IL-6 and IL-1β; decreased IL-38. On the **OI-GOUT scale**, this patient scored 12 out of 15 (high risk): maximum points for hyperuricemia, obesity, hypertension and dyslipidemia, male gender, and a history of arthritis attacks. A high score indicated active gout. This case demonstrates that the scale successfully identifies a patient with a combination of metabolic and inflammatory factors, indicating the need for active therapy. Following the scale assessment, the patient was prescribed urate-lowering therapy and given recommendations for weight loss and dietary modification, which subsequently reduced the frequency of attacks.

2. **Case Study 2 – Moderate Risk, Borderline State:** Patient K., a 59-year-old female, postmenopausal. BMI is 28 (pre-obesity), comorbidities include arterial hypertension and chronic pyelonephritis. Uric acid level is 420 μmol /L. No overt clinical episodes of gout have been previously observed, but transient knee pain periodically bothers her. According to the **OI-GOUT scale**, the total score was 7 (moderate risk): female gender (0 points for the gender factor, since the risk is lower in women), moderately elevated SUA (1 point), pre-obesity (1 point), the presence of hypertension (1 point), chronic kidney disease (small point), and age >55 (additional point) were taken into account. The patient is classified as having a moderate risk of developing gout. Although there was no overt gout at the time of assessment, the high uric acid value and comorbidities indicate a risk of a first attack. She was given preventative recommendations: a purine-restricted diet, adequate fluid intake (at least 2–2.5 liters of fluid per day, especially during hot weather), and blood pressure and weight monitoring. After a year of observation, the patient experienced her first gout attack due to poor diet and dehydration in the summer, confirming the appropriateness of her inclusion in the risk group and the importance of prevention.

3. **Case Study 3 – Low Risk, No Disease:** Patient H., a 38-year-old male, has a BMI of 24 (normal), no underlying chronic diseases, and an active lifestyle. His uric acid level is 410 μmol /L (slightly elevated). He has no complaints of joint pain and no family history of gout. His **OI-GOUT score** is 3 (low risk): small points were awarded only for moderately elevated uric acid and male gender; other factors are absent. The patient is classified as low-risk; he has not been diagnosed with gout. However, he was given lifestyle recommendations (moderately limit excessive meat and alcohol consumption, maintain fluid balance, and control his weight in the future). He has not had any gout attacks during the observation period. This case demonstrates that even in the presence of hyperuricemia without other risk factors, the likelihood of developing gout is relatively low, which is accurately reflected by the scale.

The presented clinical scenarios demonstrate the **OI-GOUT score's utility** in various situations. It allows for a quantitative assessment of a patient's predisposition to gout by integrating information on metabolic health, uric acid levels, and other important parameters. In each case, the score served as a valuable decision-making tool: from intensifying treatment in the first case to preventive monitoring in the third. Thus, **the OI-GOUT score** is suitable for use both in patients with existing gout (for complication risk stratification and disease activity monitoring) and in individuals with risk factors for gout (for early detection and prevention of disease manifestations).

Discussion

The advantages of the OI-GOUT scale are its comprehensiveness, high sensitivity and adaptability to regional conditions.

The results confirm that the developed **OI-GOUT scale** offers significant advantages over existing approaches to gout risk assessment. Unlike simplistic models based on a single indicator (e.g., uric acid levels alone), our scale is **comprehensive**. It integrates a variety of aspects—from metabolic and clinical to lifestyle—thus taking into account the multifaceted nature of gout. This approach has increased **the sensitivity** of the tool, enabling us to identify virtually all patients predisposed to or already suffering from gout. High sensitivity (93%) means that the scale is capable of capturing even the initial manifestations or combinations of risk factors that, taken together, indicate a gouty process. This is particularly important for early diagnosis and prevention: the comprehensive scale ensures **early warning** of the disease, enabling timely intervention (dietary recommendations, monitoring, preventive therapy).

At the same time, the scale's comprehensiveness did not lead to an excessive number of false-positive results— **specificity** remained at 80–85%, which is quite high for a screening tool. This was made possible by the careful selection and weighting of factors: each component contributed a statistically significant

association with gout, but no single factor (such as obesity or hyperuricemia) was so dominant as to generate a false positive without considering the context of other indicators.

The scale's adaptation to regional conditions deserves special mention**.** Our study was conducted in the Khorezm region, known for its hot climate and relative water scarcity. These environmental factors have a significant impact on gout incidence: high ambient temperatures and profuse sweating can lead to dehydration, blood thickening, and elevated uric acid levels, which trigger gout attacks. The **OI-GOUT scale** takes this into account: first, it includes questions about fluid intake and a history of dehydration/heat stress; second, when validating cutoff values, we used data obtained specifically in hot climates. This means the scale is sensitive to even a small increase in risk associated with inadequate fluid intake. Thus, **the OI-GOUT scale** is applicable to populations living in extremely hot climates (such as Khorezm) and reflects the regional risk factor profile. This distinguishes our development from other international criteria, as many international criteria do not take into account local specifics (for example, seasonal risk factors).

Overall, the advantages of the **OI-GOUT scale** —its comprehensiveness, high sensitivity, and adaptability to specific conditions—make it an effective tool for both clinical practice and epidemiological needs. It allows general practitioners and rheumatologists to more accurately assess the risk of gout in a specific patient, based on a comprehensive set of relevant data.

The role of cytokines IL-1β, IL-6 and IL-38 in pathogenesis and as biomarkers of early activity

Our study examined not only clinical and metabolic factors but also immunological markers to better understand the pathogenesis of gout and the potential for early detection of disease activity. **Interleukin-1β (IL-1β) and interleukin-6 (IL-6)** are key proinflammatory cytokines known to play a central role in the inflammatory response in gout. Monosodium urate crystals in joints activate the NLRP3 inflammasome in cells of the monocyte-macrophage lineage, leading to the release of IL-1β, the main culprit in acute gouty inflammation. IL-6 also increases following IL-1β and contributes to the maintenance of the inflammatory cascade, the acute-phase reaction (increased CRP, fever), and the recruitment of neutrophils.

In our study, we confirmed the significance of these cytokines: in patients in the study group, IL-1β and IL-6 levels were elevated 3-4-fold during the acute phase of gout compared to the control group. Even between attacks, patients with gout showed moderately elevated levels of these cytokines compared to healthy individuals, indicating persistent low-grade inflammation or the immune system's readiness to attack. Furthermore, a positive correlation was found between IL-1β concentrations and clinical gout activity ($r \approx 0.5$, $p < 0.01$): patients with more frequent/severe attacks had higher basal IL-1β levels. This confirms that IL-1β can serve **as a biomarker of activity** —its elevation signals a current or impending exacerbation.

Particular attention is paid to a new member of the IL-1 cytokine family, **interleukin-38 (IL-38) .** IL-38 is a relatively recently discovered cytokine with anti-inflammatory properties. It is considered a functional antagonist of several proinflammatory pathways: in particular, it is able to bind to IL-1 family receptors and inhibit excessive activation of immune cells. The role of IL-38 in gout is not fully understood, but our data indicate that this cytokine may be **an early marker of immune regulation imbalance** in gout predisposition. We found that serum IL-38 levels are significantly **reduced in patients with gout.** Compared to healthy individuals. Interestingly, a decrease in IL-38 was observed both during the acute period and during the remission phase (between attacks)—that is, even when there is no overt inflammation, patients with gout have baseline IL-38 levels that remain below normal. This suggests that insufficient IL-38 production is **a risk factor for the development and chronicity of gout**. A deficiency in the anti-inflammatory signal (IL-38) likely leads to a more pronounced and more severe inflammatory response to uric acid crystals, without sufficient "brakes." Furthermore, our analysis revealed an inverse relationship between IL-38 and classic inflammatory markers: low IL-38 levels were associated with higher

levels of leukocytes and CRP. Although this correlation is moderate (e.g. r≈-0.4 between IL-38 and leukocyte count), it is statistically significant ($p < 0.05$) and consistent with the hypothesis of an anti-inflammatory role for IL-38.

Thus, **IL-1β and IL-6** can be considered markers of ongoing inflammation and active gout, while **IL-38** is a potential indicator *of susceptibility to uncontrolled inflammation*. Practically, this means that measuring these cytokines (especially IL-1β) may be useful for confirming active gouty arthritis and monitoring the effectiveness of anti-inflammatory therapy (e.g., IL-1 inhibitors such as canakinumab or anakinra). At the same time, low IL-38 levels between attacks may signal the need for more aggressive urate-lowering therapy for prevention, although this concept requires further study. In the future, **IL-38 may** find use as a diagnostic biomarker for early gout activity or even as a therapeutic target (e.g., recombinant IL-38 to suppress inflammation). Our results provide a basis for such assumptions, but further studies are needed to draw definitive conclusions.

The relationship between metabolic syndrome, insulin resistance, and uric acid levels. Gout is increasingly being viewed not only as an isolated joint disease but also as part of a broader metabolic spectrum. Our data convincingly demonstrate a close link between metabolic syndrome, insulin resistance, and hyperuricemia**.** In the study group of patients, the prevalence of metabolic syndrome exceeded 60%, significantly higher than in the comparison group without gout. This means that most gout patients had multiple interrelated metabolic disorders: abdominal obesity, hypertension, dyslipidemia, and carbohydrate metabolism disorders.

The association between gout and obesity is also supported by our data: high body weight increases the production of endogenous purines and impairs kidney function, promoting the accumulation of uric acid. In the group of patients with gout, the average BMI was significantly higher, and each additional kg/m² of body area (BMI) was associated with an increase in SUA levels by ~2 μmol /L (according to the results of regression analysis). Abdominal obesity (waist circumference above the norm) correlated with the presence of gout even more strongly than overall BMI, which is consistent with the role of visceral fat in the pathogenesis (visceral adipose tissue actively produces proinflammatory adipokines and promotes insulin resistance).

Dyslipidemia, another component of metabolic syndrome, was also common in our patients. Hypertriglyceridemia was statistically significantly associated with gout: triglycerides >2.3 mmol /L were observed in almost half of the patients. Hypertriglyceridemia can reflect insulin resistance and is often associated with hyperuricemia. High triglyceride levels, as the analysis showed, increased the likelihood of belonging to the study group (OR ~1.8 when the threshold exceeded 2.3 mmol /L).

It's important to note the bidirectional nature of the relationship: on the one hand, metabolic syndrome and its components increase the risk of developing gout; on the other hand, the presence of gout (chronic inflammation and hyperuricemia) exacerbates metabolic disorders. For example, uric acid itself can contribute to oxidative stress and endothelial dysfunction, which impairs insulin sensitivity and leads to the progression of metabolic syndrome. In our study, patients with severe gout (frequent attacks, tophi) also had the most pronounced indicators of insulin resistance and dyslipidemia, indirectly confirming this vicious cycle.

The practical implication of this association is that **gout treatment should not be limited to simply lowering uric acid.** A comprehensive approach is needed, including weight management, diet, and treatment of concomitant hypertension, diabetes, and hyperlipidemia. In our study, patients who achieved at least a 5-7% weight loss and improved metabolic profile parameters during the observation period noted both a reduction in SUA levels and a decrease in the frequency of gout attacks. Thus, managing metabolic syndrome simultaneously treats and prevents gout. The **OI-GOUT scale**, which incorporates these

components, helps physicians recognize these interrelationships: a high total score directly indicates the presence of multiple factors requiring attention. This is consistent with the modern concept of gout as a " **metabolic -mediated" rheumatic disease.** Our data support this concept and demonstrate that integrating assessment of metabolic status (insulin resistance, obesity) with assessment of uric acid levels provides a more complete picture of risk than considering these factors in isolation.

Practical application of the OI-GOUT scale in outpatient and laboratory practice

One of the goals of developing the **OI-GOUT scale** was to create a tool that could be easily implemented into **daily medical practice** —both at the clinic (physician's office) and as part of laboratory screening. The results of our study demonstrate that the scale is highly informative, and the next step is its practical implementation.

In outpatient practice: In outpatient settings, general practitioners, internists, and specialists (rheumatologists, endocrinologists) can use the OI-GOUT scale to screen patients for risk factors. For example, a patient may present with complaints of intermittent joint pain in the foot, or may have no complaints at all, but is accidentally diagnosed with hyperuricemia. The doctor can quickly gather the necessary data (height, weight, blood pressure, medical history of comorbidities, recent test results) and calculate the OI-GOUT score. This requires no complex manipulation: the scale is presented as a checklist or questionnaire where the factors are noted and the score is calculated immediately. Based on this score, the doctor makes decisions:

- If the risk is high (≥9 points), refer the patient for a more in-depth examination: check for urate crystals in the joint puncture (if there has been an episode of arthritis), assess renal function, and initiate a discussion of urate-lowering therapy or prophylactic colchicine for expected attacks. Lifestyle recommendations are also mandatory, as high risk implies the presence of modifiable factors.
- For moderate risk (5-8 points), keep the patient under regular medical observation: monitor uric acid levels every 3-6 months, and track weight, blood pressure, and lipid profile. A prophylactic course of NSAIDs or colchicine may be administered at the first signs of gouty arthritis. Patient education is crucial: explaining that they are at risk and that diet and hydration can prevent the development of gout.
- For low-risk patients (<5 points), the doctor can reassure the patient that the likelihood of gout is low, but recommend periodic monitoring of key parameters (for example, a uric acid test once a year, especially if new risk factors develop). Low-risk patients do not require active intervention; general healthy lifestyle recommendations are sufficient.

Thus, **the OI-GOUT scale** serves as a kind of *navigator* for physicians, allowing them to rationally allocate their efforts: focusing on truly at-risk patients and avoiding overloading those at minimal risk with treatment. It's encouraging that the scale consists of parameters typically available in outpatient settings—anthropometry, standard blood tests, and medical history. This makes it applicable even in a typical community clinic, without the need for high-tech testing.

In laboratory practice: An interesting approach is integrating the risk score with the work of clinical diagnostic laboratories. Since some of the scale's parameters are laboratory-based (uric acid, glucose, lipids, etc.), automated gout risk calculation can be implemented when performing the relevant analyses. For example, when a patient undergoes a biochemical blood test, the laboratory information system, upon detection of hyperuricemia, could request additional data (or retrieve weight and diagnoses from the electronic patient record) and **automatically calculate the OI-GOUT score.** As a result, along with the test results, the physician receives a warning: "The patient has a high integrated risk of gout (e.g., 10 points on the OI-GOUT scale); consultation with a rheumatologist is recommended." This increases physician awareness of gout, which sometimes remains underdiagnosed, especially in its early stages, or is masked by

other problems. In addition, the laboratory can act as a screening filter: identifying individuals with asymptomatic hyperuricemia who are at high risk due to a combination of factors, and transmitting this information to treating physicians for active action.

In our pilot trial of this approach, we retrospectively applied the score to all patients whose biochemical tests showed SUA > 420 μmol /L. It turned out that approximately 30% of them had a total score above the high-risk threshold—however, not all of them had a diagnosis of gout at that time. We invited these patients for additional testing, and a number of them (about half) were found to have either incipient signs of gout (arthralgias not previously associated with gout) or significant urate deposits without overt symptoms. This suggests that **laboratory screening using the score** has the potential to detect hidden cases of gout or predictors of its rapid development.

The implementation of OI-GOUT into practice also facilitates **interdisciplinary Interaction**. For example, endocrinologists and cardiologists treating patients with metabolic syndrome, having received a gout risk assessment tool, will be able to promptly refer these patients to a rheumatologist. Conversely, a rheumatologist, seeing a patient's high risk, may recommend more frequent follow-up with a general practitioner or endocrinologist to correct metabolic abnormalities.

Finally, an important aspect is the educational aspect: the presence of a formalized scale encourages physicians to consider all the components of gout risk in every case of hyperuricemia, and patients to take the seemingly "harmless" uric acid more seriously. We have observed that when patients are clearly shown their total score and its components are explained, this increases adherence to lifestyle changes and treatment. Thus, the practical application of **OI-GOUT** not only improves gout detection and prevention but also serves as a health education tool.

In conclusion, the study results demonstrate the success of the **OI-GOUT scale**. It demonstrated high sensitivity and sufficient specificity in diagnosing gout and assessing the risk of its development, which is due to the comprehensive consideration of metabolic, clinical, and even climatic and geographical factors. The discovered relationship between immune markers (IL-1β, IL-6, IL-38) and gout activity expands our understanding of gout pathogenesis and outlines avenues for future research, including the search for new therapeutic targets. The close association of gout with metabolic syndrome indicates the need for an integrated approach to treating these patients, addressing both uric acid reduction and the correction of metabolic disorders. The **OI-GOUT scale** is designed to assist physicians in this complex task – it has already proven its effectiveness in a sample of patients in Khorezm. Further steps will be aimed at implementing the scale in practice through physician education and the development of user-friendly digital tools. We are confident that the widespread use **of OI-GOUT will improve the quality of prevention and early detection of gout, especially in regions with a high prevalence of this disease and its risk factors.**

Conclusions:

1. For the first time, the integrated clinical and laboratory scale **OI-GOUT (Oyghul) was developed and tested Ikramovna – Gout Risk & Prognosis Tool,** designed for **early diagnosis and risk stratification of gout** in outpatient settings. The scale combines clinical data, medical history, metabolic parameters, lifestyle, inflammatory markers, and environmental factors.
2. The scale is structured in six blocks (A–F), reflecting key domains of disease pathogenesis, and allows for the automatic calculation of **a total risk score (0–40)** with subsequent distribution of the patient into **five risk levels** —from minimal to very high.
3. Validation conducted on a sample of **176 patients** (including 97 patients with gout and 79 individuals without the diagnosis) demonstrated high diagnostic accuracy of the scale: **AUC = 0.91**, sensitivity 93%,

specificity 85%, PPV 88%, NPV 91%. This indicates its suitability for both screening and clinical decision-making.

4. A high score on the OI-GOUT scale was associated not only with the presence of gout, but also with the severity of **metabolic syndrome, insulin resistance, and hyperuricemia**, confirming the relationship between these conditions and justifying the need for complex therapy.
5. **Cytokine markers (IL-1β, IL-6, IL-38)** showed a special significance in early diagnosis and prognosis: IL-1β and IL-6 increased during exacerbation of gout, and a decrease in IL-38 correlated with the risk and severity of the course, opening up prospects for an immunomodulatory approach in treatment.
6. The scale demonstrated adaptation to **the hot and arid climate of the Khorezm region**, taking into account regional characteristics of nutrition, drinking regime, access to medical care and environmental stress.
7. The scale's practical applicability has been confirmed: it is available as **offline and web-based tools** with the ability to be integrated into laboratory and outpatient practices. This creates the basis for its implementation in routine medical care, as well as for future large-scale studies and inclusion in national guidelines.
8. Thus, **OI-GOUT** is a reliable, validated and clinically relevant tool to improve the effectiveness of early detection, prevention and management of gout at the population level, especially in regions with a high prevalence of metabolic disorders.

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