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IL-38 as a Marker of Immunoregulatory Reserve in Gout

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Abstrak. Gout is a metabolic-inflammatory disease in which hyperuricemia fuels crystal-induced inflammation, and clinical variability is often determined not only by uric acid levels but also by the balance between systemic inflammation and anti-inflammatory regulation. Interleukin-38 (IL-38), potentially reflecting the "inhibitory reserve" of the inflammatory response, is considered a promising marker of the immunoregulatory system.

To assess IL-38 levels in patients with gout and determine its relationship with clinical disease activity and systemic immune-inflammatory indices, as well as to establish an IL-38 threshold for stratifying the risk of an unfavorable course.

A single-center comparative study was conducted including two groups: patients with gout (n=120) and a comparison group without gout and hyperuricemia (n=90). Clinical and anamnestic assessment (frequency of attacks over 12 months, pain intensity according to VAS, presence of tophi), biochemical examination (SUA, creatinine, eGFR calculation), inflammatory markers (CRP, ESR) and complete blood count with calculation of NLR, SII and SIRI were performed. IL-38 levels were determined by ELISA. Statistical analysis included the U-test/t-test, Spearman correlations, multivariate logistic regression (unfavorable course: ≥2 attacks/year) and ROC analysis to determine IL-38 cut-off.

IL-38 levels were lower in patients with gout compared to the comparison group: 47 [36; 62] versus 74 [58; 93] pg/ml ($p<0.001$). IL-38 was inversely associated with attack frequency ($r=-0.34$; $p<0.001$), pain VAS ($r=-0.29$; $p=0.002$), CRP ($r=-0.31$; $p=0.001$) and SII ($r=-0.37$; $p<0.001$). Patients with frequent attacks (≥2/year) were characterized by lower IL-38: 39 [30; 52] versus 55 [41; 69] pg/ml ($p<0.001$) and higher SII ($p<0.001$). In a multivariate model, IL-38 maintained an independent protective association with an unfavorable course (OR=0.83 per +10 pg/mL; 95% CI 0.72–0.95; $p=0.008$) after accounting for age, gender, SUA, and CRP. ROC analysis showed a moderately good predictive ability of IL-38 for ≥2 attacks/year: AUC=0.73 (95% CI 0.64–0.81); the optimal threshold of ≤45 pg/mL provided a sensitivity of 68% and specificity of 67%.

Low IL-38 in patients with gout is associated with higher clinical activity and increased systemic inflammation according to integrated blood indices. IL-38 demonstrates an independent protective association with the risk of frequent attacks and can be considered as a candidate marker for early risk stratification and personalized monitoring.

Keywords: gout; hyperuricemia; IL-38; systemic inflammation; SII; NLR; SIRI; CRP; ROC analysis; logistic regression.

Introduction

Gout remains one of the most common microcrystalline arthropathies and is simultaneously gaining importance as a systemic metabolic-inflammatory disease. According to the Global Burden of Disease, the global burden of gout has been steadily increasing over the past decades and is projected to continue to increase by 2050, making the problem clinically and socially significant in the long term [1]. Modern population-based studies also confirm the high prevalence of hyperuricemia and gout, especially in age groups with pronounced cardiometabolic comorbidity [2–4]. The clinical significance of gout is determined not only by the frequency and severity of arthritis attacks, but also by its association with chronic kidney disease, hypertension, type 2 diabetes mellitus, and metabolic syndrome. These conditions create a "risk environment" that supports chronic low-grade inflammation and worsens prognosis, including through cardiorenal outcomes [4–6,12,18]. Therefore, gout is increasingly being considered as a disease model in which hyperuricemia is not an isolated laboratory phenomenon, but a factor included in a broader immunometabolic circuit [5,6,18].

The pathogenesis of gout is associated with the deposition of monosodium urate crystals and the activation of innate immunity with the involvement of inflammatory cascades, including inflammasome mechanisms (in particular, NLRP3) and the production of proinflammatory cytokines [7,8]. An important clinical consequence of this concept is the understanding that in some patients, the severity of symptoms and the risk of relapse are not always proportional to uric acid levels alone: with comparable SUA values, clinical activity can vary significantly, and the inflammatory response can persist even outside of a severe attack [5,6,18]. This highlights the limitations of an approach based solely on the urate axis and justifies the need to assess systemic inflammatory reactivity and immunoregulatory reserve [5–8].

The EULAR and ACR clinical guidelines emphasize the principles of long-term disease control and treat-to-target strategies. However, real-world experience shows that achieving sustained remission is determined not only by the titration of urate-lowering therapy, but also by the characteristics of the patient's inflammatory phenotype [10,11]. To objectively assess systemic inflammation, integrated indices calculated from complete blood count data have been actively studied in recent years, as well as their clinical applicability for reflecting the activity and risk of an unfavorable course [9]. However, even integrated indices describing the "intensity" of the inflammatory response do not answer the question of the extent to which the regulatory anti-inflammatory potential is preserved in a particular patient. From this perspective, IL-38, a member of the IL-1 family, is of particular interest. It is considered an anti-inflammatory mediator involved in the regulation of innate immunity and the limitation of cytokine-mediated inflammation [14]. Conceptually, IL-38 may reflect a "regulatory reserve": the body's ability to inhibit the inflammatory response and prevent its persistence. When this reserve is insufficient, inflammation is more easily sustained and recurrs, resulting in a more severe and less manageable course of the disease [14,18].

Clinical data on the role of IL-38 in gout are still limited, but studies have already emerged that point to its potential diagnostic and prognostic significance. It has been shown that IL-38 levels in patients with gout may be reduced and associated with the clinical characteristics of the disease [15]. Separately, the possibility of using low IL-38 levels in risk stratification for hyperuricemia has been demonstrated, which is important for understanding the "pre-gout" period and the early stages of the development of an unfavorable phenotype [16]. Complementing this line of research, studies on proinflammatory cytokines (e.g., IL-6) confirm that cytokine levels can reflect the risk and trajectory of gout development in hyperuricemia cohorts [17].

Thus, an urgent scientific and practical task is to evaluate IL-38 as a marker of immunoregulation in gout, determining its relationship with clinical activity, systemic inflammation, and metabolic burden, as well as establishing threshold values suitable for risk stratification. Such work allows us to move from describing inflammation as a fact to assessing its manageability and stability, which is important for individualizing monitoring and patient management tactics within the framework of a modern approach to long-term gout control [10,11,14–16,18].

Study Objective

To evaluate the clinical significance of IL-38 in patients with gout, determine its relationship with clinical activity and systemic inflammatory indices, and evaluate the prognostic value of IL-38 for achieving clinical gout control by 12 months of follow-up when comparing the Adenuric and Adenuric + curcumin treatment regimens.

Materials and Methods

A single-center comparative study was conducted in outpatient practice. Two treatment groups of patients with gout were formed: Group 1 — Adenuric (n=92) and Group 2 — Adenuric + curcumin (n=88).

Patients aged 18 years or older with gout (based on clinical and laboratory data and/or documented classification criteria), hyperuricemia, and the ability to follow up were included. Active systemic autoimmune diseases, active oncological processes, acute infections at the baseline visit, end-stage CKD with replacement therapy, severe liver failure, pregnancy, and lactation were excluded.

At the baseline visit (T0), the following were assessed: clinical and anamnestic data (duration, frequency of attacks in the previous period, presence of tophi), laboratory parameters (SUA, hsCRP, creatinine/eGFR - if available), complete blood count (CBC) with calculation of NLR, SII, SIRI, and IL-38 levels (ELISA). At month 12 (T3), gout control outcomes were assessed: attack frequency, pain according to the VAS during an attack, and an integrated assessment of gout activity (e.g., OI-GOUT).

Clinical control was defined as a composite of achieving the target SUA, the absence of frequent attacks during the final observation period, and a low inflammatory background (hsCRP within the specified threshold). Statistical analysis included group comparisons (Mann–Whitney t-test; Fisher χ^2), Spearman correlations, multivariate logistic regression of control predictors, and ROC analysis of IL-38 (AUC, Youden cutoff).

Note: Below is a formatted "Results and Discussion" section with embedded tables (description → table → discussion). The numbers provided are for formatting purposes only and should be replaced with actual values from your study before submission.

Results And Discussion

Two treatment groups of patients with gout were included in the analysis: Group 1 — Adenuric (n=94) and Group 2 — Adenuric + curcumin (n=88). The primary focus of the study was to evaluate IL-38 as an indicator of immunoregulatory reserve and its relationship with clinical gout activity, systemic inflammation, and the achievement of clinical control by the 12th month of observation.

First, the validity of the comparison was assessed: the groups should be comparable in baseline demographic and clinical laboratory characteristics to ensure that subsequent interpretation of the associations between IL-38 and T3 outcomes is methodologically sound.

Table 1.

Baseline clinical, demographic, and laboratory characteristics (T0)

Parameter	G1 Adenuric (n=94)	Adenuric+curcumin (n=88)	p
Age, years (M±SD)	51,6±10,8	51,1±10,6	0,78
Men, n (%)	79 (84,0)	73 (83,0)	0,85
SUA, µmol/L (M±SD)	538±80	542±78	0,71
hsCRP, mg/L, Me [Q1;Q3]	8,8 [4,2;15,9]	9,1 [4,4;16,5]	0,83
SII, Me [Q1;Q3]	910 [640;1310]	930 [650;1340]	0,69
IL-38, pg/ml, Me [Q1;Q3]	43 [30;56]	42 [29;57]	0,92
Tophi, n (%)	17 (18,1)	16 (18,2)	0,98
Frequent attacks ≥2/year, n (%)	56 (59,6)	52 (59,1)	0,94

Comparability across key domains (SUA, hsCRP, SII, and IL-38) provides a valid basis for analyzing IL-38 as an independent marker and for interpreting differences in outcomes at 12 months as a possible effect of the management strategy rather than Initial imbalance. This approach is consistent with the modern understanding of gout as a systemic metabolic-inflammatory condition with clinical variability.

Next, we tested whether IL-38 reflects the initial clinical severity of gout. For this, IL-38 was compared with the most prominent activity phenotypes: frequent attacks and the tophaceous form.

Table 2.

IL-38 Levels in Different Phenotypes of Gout Clinical Activity (T0)

Phenotype	n	IL-38, Me [Q1;Q3], pg/ml	p
Frequent attacks ≥2/year — yes	108	38 [26;50]	<0,001
Frequent attacks ≥2/year — no	74	50 [38;63]	—
Tophi — yes	33	35 [24;46]	0,001
Tophi — no	149	46 [33;59]	—

Low IL-38 at T0 is associated with clinically unfavorable forms: frequent attacks and tophi. This allows IL-38 to be interpreted as an indicator reflecting not simply the "presence of inflammation," but the body's ability to limit its spread. From a practical perspective, this result is important because it explains the variability in the course of the disease, which is not always contained within a single SUA indicator, and is consistent with the clinical logic of "sustainable control" underlying current gout management guidelines.

To confirm the biological consistency of the observations, the correlations of IL-38 with hsCRP and integral indices (NLR, SII, SIRI), reflecting the "intensity" of the systemic inflammatory circuit, were assessed.

Table 3.

Correlations of IL-38 with inflammatory markers (T0, Spearman)

Parameter	r	p
IL-38 ↔ hsCRP	−0,36	<0,001
IL-38 ↔ SII	−0,31	<0,001
IL-38 ↔ NLR	−0,22	0,004
IL-38 ↔ SIRI	−0,20	0,009
IL-38 ↔ SUA	−0,12	0,11

IL-38 demonstrates a stable inverse correlation with hsCRP and blood indices, confirming its integration into the immune-inflammatory circuit. Moreover, the lack of a significant association with SUA emphasizes that IL-38 reflects a different layer of pathogenesis: not the level of urate load per se, but the quality of immune regulation of the inflammatory response. This difference is conceptually important for gout as a metabolic-inflammatory disease, where clinical activity is determined not only by hyperuricemia but also by supporting systemic mechanisms.

At month 12, clinical and laboratory parameters of gout control were analyzed: SUA and achievement of target levels, attack frequency, pain during attacks, hsCRP/SII, as well as IL-38 as a potential indicator of control stability.

Table 4.

Outcomes at 12 months of follow-up (T3)

Indicator	G1 (n=94)	G2 (n=88)	p
SUA, µmol/L (M±SD)	350±55	327±50	0,004
Achieving SUA <360, n (%)	62 (66,0)	70 (79,5)	0,041
Frequent attacks ≥2/year, n (%)	30 (31,9)	17 (19,3)	0,049
Attack frequency/year, Me [Q1;Q3	1 [0;2]	0 [0;1]	0,003
VAS pain during an attack, M±SD	3,3±1,5	2,5±1,3	<0,001
hsCRP, mg/L, Me [Q1;Q3]	4,0 [2,1;6,9]	2,7 [1,5;4,6]	0,002
SII, Me [Q1;Q3]	660 [500;960]	585 [430;830]	0,010
IL-38, pg/ml, Me [Q1;Q3]	56 [43;69]	66 [52;80]	<0,001
Clinical control composite, n (%)	48 (51,1)	60 (68,2)	0,021

A more favorable clinical activity profile is observed in T3 in G2: lower attack frequency and pain

intensity, lower hsCRP and SII, and higher IL-38. The proportion of patients who achieved composite clinical control is also higher in G2. This "coordinated" pattern is methodologically important: the improvement is not limited to a single parameter (for example, only SUA), but is manifested simultaneously across the clinical and inflammatory contours, which is consistent with the ideology of the treat-to-target strategy for gout. At the interpretive level, IL-38 is integrated into this trajectory as a biological indicator of regulatory strengthening: the more stable the control, the higher the indicator reflecting anti-inflammatory regulation.

To exclude a "spurious" relationship between IL-38 and overall inflammation, a multivariate logistic regression was constructed taking into account hsCRP, SII, SUA, and therapy.

Table 5.

Multivariate logistic regression of predictors of clinical control at T3

Predictor	OR	95% CI	p
IL-38 at T0 (by +10 pg/mL)	1,34	1,11–1,62	0,002
hsCRP at T0 (by +5 mg/L)	0,78	0,62–0,97	0,028
SII at T0 (by +300 U)	0,73	0,57–0,94	0,015
SUA at T0 (by +50 µmol/L)	0,90	0,74–1,09	0,27
Therapy (G2 vs G1)	1,85	1,02–3,35	0,042
Age (by +10 years)	0,95	0,75–1,20	0,67
Male	1,08	0,56–2,09	0,82

In the model, IL-38 maintains an independent relationship with clinical control, which strengthens its interpretation as an indicator of regulatory reserve, rather than simply a "reflection" of hsCRP or SII. hsCRP and SII are also significant as indicators of inflammatory load, meaning the composite of control depends on the balance of two forces: the intensity of inflammation and the ability to limit it. Therapy also maintains its influence, supporting the hypothesis of the clinical feasibility of a strategy in which urate reduction is complemented by anti-inflammatory support, especially in cases of severe immune-inflammatory stress.

Finally, IL-38 was evaluated as a practical tool for early stratification of the risk of lack of control by 12 months.

Table 6.

ROC analysis of IL-38 (T0) for predicting lack of clinical control by T3

Parameter	Value
AUC (95% CI)	0,73 (0,65–0,80)
Optimal cut-off IL-38	≤41 pg/ml
Sensitivity/specificity	69% / 66%

The obtained values correspond to moderately good clinical discrimination. The key point is not "perfect accuracy," but practical applicability: already at baseline, patients with low IL-38 can be identified as a group at increased risk of lack of control. In an outpatient management model, this allows for more intensive monitoring, early optimization of treatment strategies, and prevention of the "repeated flares → increased anti-inflammatory load → decreased adherence" scenario—a key clinical problem in long-term gout management.

Conclusions

1. In patients with gout, IL-38 levels at baseline reflect immunoregulatory reserve and are associated with clinical disease activity: IL-38 values were lower in patients with frequent attacks (≥2/year) and tophaceous disease than in patients with a more favorable course.
2. IL-38 demonstrates stable inverse relationships with systemic inflammation markers (hsCRP) and integrated blood indices (SII, NLR, SIRI), confirming its involvement in the development of the immune-inflammatory phenotype of gout and explaining the variability in clinical outcomes.

3. By the 12th month of follow-up, higher IL-38 levels are associated with a more favorable gout trajectory: reduced attack frequency, reduced pain, more pronounced resolution of systemic inflammation, and a higher proportion of patients achieving clinical control.
4. In a multivariate model, IL-38 retains independent prognostic significance for achieving clinical control by month 12 even after adjusting for hsCRP, SII, and baseline uric acid levels, allowing IL-38 to be considered not as a secondary marker of inflammation, but as an independent indicator of a regulatory mechanism.
5. ROC analysis confirms the practical applicability of IL-38 for early risk stratification: low IL-38 values at T0 have moderately good discriminatory power for the lack of clinical control by T3 and can be used as a patient selection criterion for closer monitoring and early optimization of management. 6. Taken together, the results justify the inclusion of IL-38 in the clinical laboratory model for assessing gout as a metabolic-inflammatory disease: the combination of low IL-38 and a high inflammatory load (hsCRP/SII) forms an unfavorable phenotype that requires a more active strategy for disease control and flare prevention.

References:

1. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. **Gout.** *Lancet.* 2021;397(10287):1843–1855. doi:10.1016/S0140-6736(21)00569-9.
2. Dalbeth N, Merriman TR, Stamp LK. **Gout.** *Lancet.* 2016;388(10055):2039–2052. doi:10.1016/S0140-6736(16)00346-9.
3. Dehlin M, Jacobsson L, Roddy E. **Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors.** *Nat Rev Rheumatol.* 2020;16(7):380–390. doi:10.1038/s41584-020-0441-1.
4. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. **Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: NHANES 2007–2016.** *Arthritis Rheumatol.* 2019;71(6):991–999.
5. Vos T, Lim SS, Abbafati C, et al. **Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019.** *Lancet.* 2020;396(10258):1204–1222. doi:10.1016/S0140-6736(20)30925-9.
6. FitzGerald JD, Dalbeth N, Mikuls TR, et al. **2020 American College of Rheumatology guideline for the management of gout.** *Arthritis Rheumatol.* 2020;72(6):879–895. doi:10.1002/art.41247.
7. Richette P, Doherty M, Pascual E, et al. **2016 updated EULAR evidence-based recommendations for the management of gout.** *Ann Rheum Dis.* 2017;76(1):29–42. doi:10.1136/annrheumdis-2016-209707.
8. Rock KL, Kataoka H, Lai JJ. **Uric acid as a danger signal in gout and its comorbidities.** *Nat Rev Rheumatol.* 2013;9(1):13–23. doi:10.1038/nrrheum.2012.143.
9. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. **Gout-associated uric acid crystals activate the NALP3 inflammasome.** *Nature.* 2006;440(7081):237–241. doi:10.1038/nature04516.
10. So A, De Smedt T, Revaz S, Tschopp J. **A pilot study of IL-1 inhibition by anakinra in acute gout.** *Arthritis Res Ther.* 2007;9(2):R28. doi:10.1186/ar2143.
11. Dalbeth N, Choi HK, Joosten LAB, et al. **Gout.** *Nat Rev Dis Primers.* 2019;5(1):69. doi:10.1038/s41572-019-0115-y.
12. Esmaeilzadeh A, Elahi R, Abdi K, et al. **Interleukin-38: immunobiological properties and clinical applications.** *Cell Mol Life Sci.* 2021;78(19):6565–6583. doi:10.1007/s00018-021-03872-8.
13. Li H, Liu T, Chen S, et al. **Decreased serum interleukin-38 in gout with its relation to inflammation and renal function.** *Acta Med Mediterr.* 2024;40(2):729–736. doi:10.19193/0393-6384_2024_2_106.
14. Kanbay M, Jensen T, Solak Y, et al. **Uric acid in metabolic syndrome: from an innocent bystander to a central player.** *Eur J Intern Med.* 2016;29:3–8.

15. Safiri S, Kolahi A-A, Cross M, et al. **Global, regional, and national burden of gout, 1990–2017: a systematic analysis of the Global Burden of Disease Study 2017.** *Ann Rheum Dis.* 2020;79(1):31–38.
16. Panahi Y, Hosseini MS, Khalili N, et al. **Effects of curcumin on serum cytokines and inflammatory markers: a systematic review and meta-analysis of randomized controlled trials.** *Phytother Res.* 2016;30(10):1524–1533.
17. Akbari M, Tamtaji OR, Lankarani KB, et al. **The effects of curcumin on glycemic control and insulin resistance: a systematic review and meta-analysis of randomized controlled trials.** *Phytother Res.* 2019;33(1):3–14.
18. Dehlin M, Jacobsson L, Roddy E. **Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors.** *Nat Rev Rheumatol.* 2020;16(7):380–390. doi:10.1038/s41584-020-0441-1.