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# Combination of Irisin, Uric Acid, and Pro-Inflammatory Cytokine To Distinguish Gout Patients From Healthy Controls in The Governorate of Thi-Qar

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## Abstract

This study aimed to investigate the potential of combining uric acid levels with pro-inflammatory cytokines, specifically interleukin-1β (IL-1β) and the myokine irisin, to enhance the precision of gout diagnosis. The patient group comprised 80 individuals with gout, while the control group included 70 healthy subjects. Serum levels of IL-1β and irisin were measured in both groups, and Pearson correlation analysis was employed to assess their relationships with serum uric acid. Results revealed that gout patients exhibited significantly higher levels of IL-1β and serum uric acid but lower irisin levels compared to the control group. Negative correlations were observed between irisin and IL-1β, as well as between irisin and uric acid. Conversely, a positive correlation was found between serum uric acid and IL-1β. Receiver operating characteristic (ROC) curve analysis demonstrated high diagnostic accuracy for both IL-1β and irisin in discriminating gout patients from healthy individuals, suggesting their potential utility as diagnostic indicators for gout. This study underscores the promise of combining IL-1β, irisin, and uric acid measurements to enhance the accuracy of gout diagnosis, paving the way for further multicenter trials to validate this approach's effectiveness.

**Highlights:**

- **Novel Diagnostic Approach:** This study proposes a novel diagnostic approach for gout by combining serum levels of uric acid with pro-inflammatory cytokines IL-1β and myokine irisin, demonstrating its potential to enhance precision.
- **Correlation Insights:** The study reveals significant correlations between uric acid, IL-1β, and irisin levels, shedding light on the intricate relationship between inflammation, myokines, and gout pathophysiology.
- **Diagnostic Accuracy:** High diagnostic accuracy, as indicated by ROC curve analysis, underscores the clinical utility of IL-1β and irisin as potential indicators for gout diagnosis, offering a promising avenue for improved clinical assessment.

**Keywords:** Gout Diagnosis, Interleukin-1β, Irisin, Uric Acid, Pro-Inflammatory Cytokines.

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# Introduction

The buildup of monosodium urate (MSU) crystals in the tissues and joints causes gout. The most common kind of arthritis is inflammatory, sometimes known as gout[1]. gout affects around 2-4% of the population, and since its prevalence has increased recently, the harm it does to public health has been greater[2][3]. Hyperuricemia is a necessary prerequisite for gout arthritis (GA), which necessitates it. MSU crystals, among other things, can activate the macrophage NLRP3 inflammasome, which in turn stimulates the production of pro-inflammatory substances including interleukin-1β (IL-1β)[4]. These pro-inflammatory substances cause the activation and recruitment of extra neutrophils and monocytes, which in turn causes those cells to produce further pro-inflammatory cytokines. Finally, the cascade effect of this inflammatory reaction leads to gouty episodes[4].

The primary producers of the pro-inflammatory cytokine IL-1β are monocytes and macrophages. Numerous studies have shown that IL-1β is crucial for GA attacks and tissue damage[5][6]. Infectious, inflammatory, autoimmune, and degenerative disorders are all caused by IL-1β, which is produced by a diverse range of cell types. Gout flare-ups' pathophysiology depends on IL-1β[7]. Pro-IL-1 β must be activated by either IL-1 receptors or pattern recognition receptors (PRRs) because it is not constitutively produced. Free fatty acids are one example of an endogenous stimulus that can activate PRRs and cause IL-1β to be translated into an inactive precursor[8]. Caspase 1 cleaves the precursor IL-1β because it is already active in monocytes. Caspase-1 must be turned on from its latent condition in macrophages using the NLRP3 inflammasome, according to[9]. By altering several intracellular networks, such as those that encourage autophagy failure, create oxidative stress, and prevent AMP-activated protein kinases (AMPK), MSU crystals produce NLRP3 inflammasomes and enhance inflammation[8].

Gout flares are characterized by a substantial influx of neutrophil into the affected joint when the inflammatory process begins. By exploiting various proteolytic breaking sites of caspase 1, when the serine proteases, which cathepsin G, neutrophil elastase, and the proteinase 3 convert inactive IL-1 precursor into active IL-1, they contribute significantly to the fast synthesis of mature IL-1 and subsequent inflammatory reactions[10]. The intercritical phases of gout are characterized by an elevated level of pro-inflammatory cytokines, and IL-1β not only contribute to the pathophysiology of gout flares but is also connected to hyperuricemia[11]. The NLRP3 inflammasome, MAP kinases, and AMPK are all activated by soluble urate, and it also inhibits AMPK, which indirectly stimulates Mtor[8].

Irisin belongs to the myokine family a group of growth factors and cytokines whose main organ of target is skeletal muscle and where they are mostly expressed. The peroxisome proliferator-activated receptors coactivator 1 (PGC-1) develops mostly in skeletal muscle as a result of exercise and exposure to cold[12]. Irisin may improve mogenesis and energy expenditure by increasing the synthesis of uncoupling proteins (UCP1)1 and browned of white adipose cells within adipose tissue[13]. It is a hormone created from FNDC5, a protein that contains the fibronectin type three domain. According to some research[14], aerobic exercise does not necessarily activate the FNDC5 gene in younger humans. Regular exercise was also found to be negatively correlated with the concentration of the hormone irisin in adult men[15]. These inequalities may be explained through knowing that individuals who lead sedentary lives have a quick decline in muscles concentrations of ATP in the absence of exercise since irisin levels can only increase when more energy is required[16].

The purpose of study to determine if cytokines that are pro-inflammatory and uric acid concentration may be used in conjunction to improve the accuracy of gout diagnosis.

# Method

## Design of study

In this study, 150 specimens were collected from specialist clinics and the Al-Hussein Teaching Hospital in the Thi-Qar Governorate of Iraq during the months of August 2021 and Septembers 2022, with the range of ages being 20 to 90 year. . Blood samples from 110 patients were used ; 80 of them had gouty diagnoses, 30 were excluded. All participants underwent a thorough clinical examination, the details of the numbers and age of the table 1.

| Groups | Age (years) | No. |
|---|---|---|
| | 20- 44 | 80 |
| Gout Patients | 45- 69 | 80 |
| | 70 -94 | 80 |
| | 20- 44 | 70 |
| Control | 45 -69 | 70 |
| | 70 - 94 | 70 |

**Table 1.** *Details of numbers and age of the studied groups*

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## Blood Sample Collection:

Each patient's venous blood sample (5 ml) was taken and put into a gel tube at room temperature, after which it was separated in a centrifuge for 10 minutes at 3000 rpm. The separated serum was split, and pooled in Eppendorf tubes, then freezen, and kept at -20 Ċ, until use unless immediately used to evaluate biochemical parameters.

## Measurment s

Each sample's analyte concentration was automatically determined by a Roche/Hitachi Cobas C311 system, which also measured the levels of serum uric acid (German - Japan). Additionally, the Enzyme-Linked Immunosorbent Assay, which is a commercially accessible (ELISA) kit with the Cat Nos. (E0143Hu) and (E3253Hu) of the Bioassay Technology Laboratory (BT LAB) were used to assess the amounts of IL-1β and irisin utilized to evaluate them, respectively. IL-1β and irisin (BTLAB/China), as directed by the manufacturer.

## Statistica l analy sis

The data were acquired, processed, summarized, analyzed, and presented using SPSS version 26 and Excel from Microsoft Office 2010. The distribution of the numerical data was examined using the Kolmogorov-Smirnov test. Then it was followed by the mean and standard deviation. If the variable is regularly distributed, a t-test with an independent sample was employed to arrive at the mean difference among the two groups. Examining the average variance among more than two groups using the ANOVA test is one use when the variable is normally distributed. The test known as the chi-square test was employed to look for correlations between any two category variables. In order to evaluate the risk, a 95% confidence interval was used. The results were presented as the correlation coefficient (r) and the level of significance (P), and they may be any two numerical variables. The receiver operators characteristics (ROC) curve analysis was used to determine the cutoff value that reliably predicts a positive discovery (P), as well as its accuracy level, specificity, sensitivity, and level of significance[17]. P-values below 0.01 were considered to be highly significant, while P-values below 0.05 were considered to be significant as well as p-values higher than 0.05 were considered to be no significant.

# Results and Discussion

## Levels of a few indicators in gout patients and healthy controls

**Serum uric acid concentration in gout patients and in healthy controls**

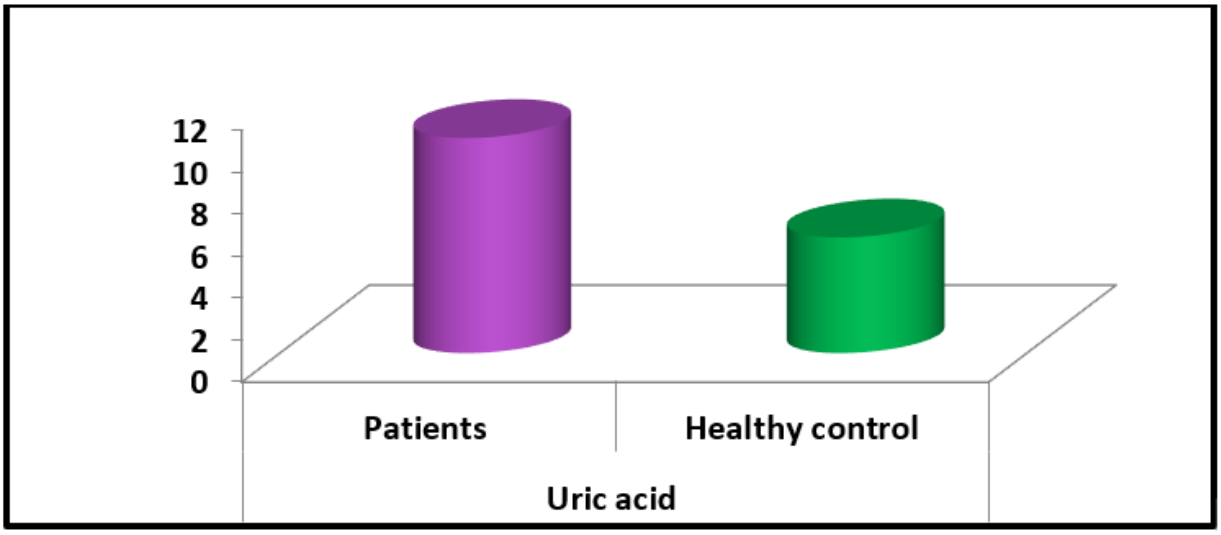


**Figure 1.** *Mean Levels of Parameters (Uric Acid)According to study Groups*

Figure 1 and Table (2). According to the current findings, gout patients exhibited considerably higher mean serum uric acid levels than healthy control subjects, 10.23 ± 1.44 versus 5.50 ± 1.21 respectively, (P <0.001).

| | Cases –control comparison | |
|---|---|---|

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| | Patients n = 80 | Healthy control n = 70 | P |
|---|---|---|---|
| Uric acid (mg/dl) | | | |
| Mean± SD | 10.23 ± 1.44 | 5.50 ± 1.21 | < 0.001 † HS |
| Range | 7.80 -13.40 | 3.50-7.50 | |

**Table 2.** *Mean Levels of Parameters (Uric acid )According to study Groups*

n: number of cases, SD is for standard deviation, t stands for independent samples t-test, and HS stands for highly significant at P 0.001.

## Subjects Immunological Analysis Results

**Serum Interleukin-1β (IL-1β) level in patients with gout and healthy control**

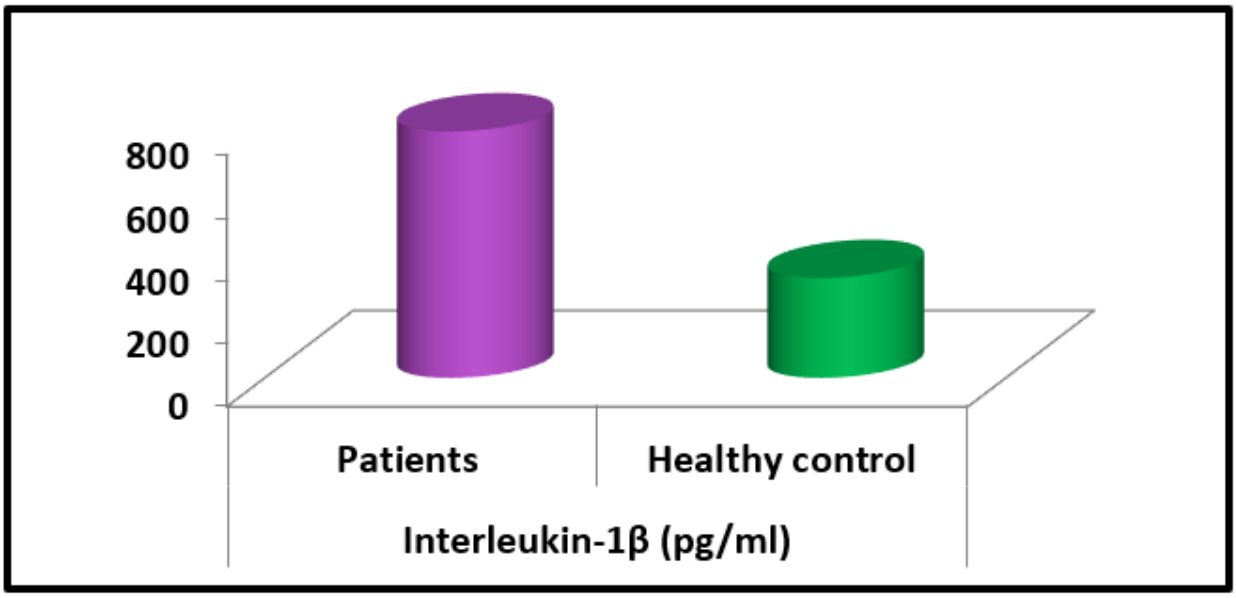


**Figure 2.** *Mean serum IL-1 β levels for normal controls and patients*

The outcomes were present in table (3) and figure (2). In healthy controls and gout patients, the mean serum IL-1β levels were 781.88 ± 314.45 pg/ml and 316.79 ± 94.85 pg/ml, respectively, the difference among the two was showed highly significant (P 0.001), and higher in gout patients.

| | Cases –control comparison | | |
|---|---|---|---|
| | Patients n = 80 | Healthy control n = 70 | P |
| Interleukin-1β (pg/ml) | | | |
| Mean± SD | 781.88 ± 314.45 | 316.79 ± 94.85 | < 0.001 † HS |
| Range | 434.31 – 1845.87 | 188.41- 499.48 | |

**Table 3.** *Serum Interleukin-1β (IL-1 β) level in gouty patients and healthy control*

n: number of cases, SD is for standard deviation, t stands for independent samples t-test, and HS stands for highly significant at P 0.001.

**Serum irisin level in gouty patients and healthy control**

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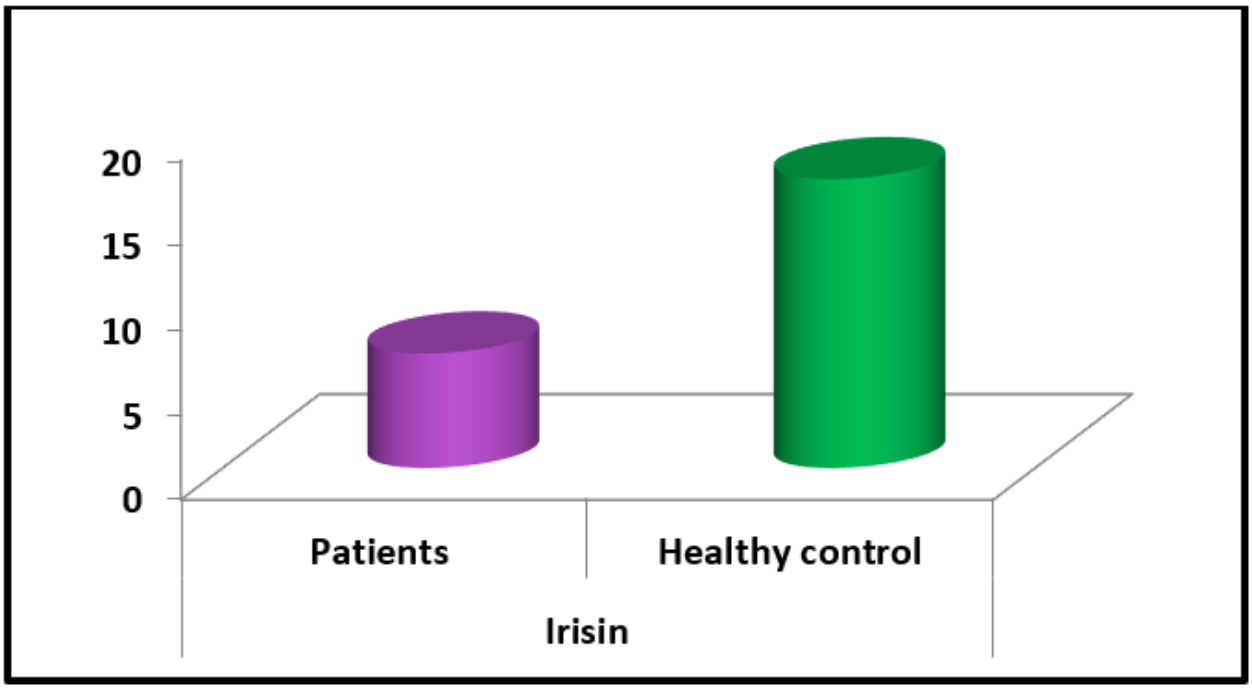


**Figure 3.** *Mean serum Irisin levels for normal controls and patients*

Explain Table (4) and Figure (3). found in gout patients and healthy controls, the mean levels of serum irisin were 6.76 2.91 ng/ml and 17.03 4.14 ng/ml, respectively; the level was significantly lower in gout patients than in healthy controls (P <0.001).

| | Cases –control comparison | | |
|---|---|---|---|
| | Patients n = 80 | Healthy control n = 70 | P |
| Irisin (ng/ml) | | | |
| Mean± SD | 6.76 ± 2.91 | 17.03 ± 4.14 | < 0.001 † HS |
| Range | 2.12 – 13.24 | 12.99-29.09 | |

**Table 4.** *Serum Irisin level in patients with healthy control and gout*

***n:*** number of cases, **SD** is for standard deviation, **t** stands for independent samples t-test, and **HS** stands for highly significant at P 0.001**.**

## Correlations between different parameters

The correlations between immunological parameters and biochemical parameters levels are shown in Table (5).

| Characteristics | | IL-1β | Irisin |
|---|---|---|---|
| IL-1β | R | 1 | -0.080 |
| | P | | 0.481 |
| U. Acid | R | 0.101 | -0.023 |
| | P | 0.895 | 0.842 |

**Table 5.** *Correlations between IL-1β, Irisin , and U. Acid in gouty patients*

## Pro-inflammatory cytokines and serum uric acid levels have diagnostic value in gout patients

### Evaluation of IL-1β

Using diagnostic or supplementary tests, receiver operators characteristics (ROC) curves analysis was carried out to assess the IL-1β cutoff values and to predict the existence of gout. Table (6) and Figure (6) present the findings

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(4). The cutoff for IL-1β had a cutoff value of > 436.16-fold and specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), and area under the curve of 98.8%, 88.6%, 90.4%, 98.4% and 0.990 (0.979-1.000).

| IL-1 β level | Gout patients n = 80 | Healthy control n = 70 |
|---|---|---|
| > 436.16 | 79 (%) | 8 (%) |
| > 436.16 | 1 (%) | 62 (%) |
| Sensitivity % | 98.8 % | |
| Specificity % | 88.6% | |
| PPV % | 90.8% | |
| NPV % | 98.4% | |
| AUC ( 95 % CI ) | 0.990 (0.979- 1.000) | |

**Table 6.** *Specificity and sensitivity of IL-1 β level (> 436.16-fold) in gout disease*

CI is for confidence interval, while AUC stands for area under curve.

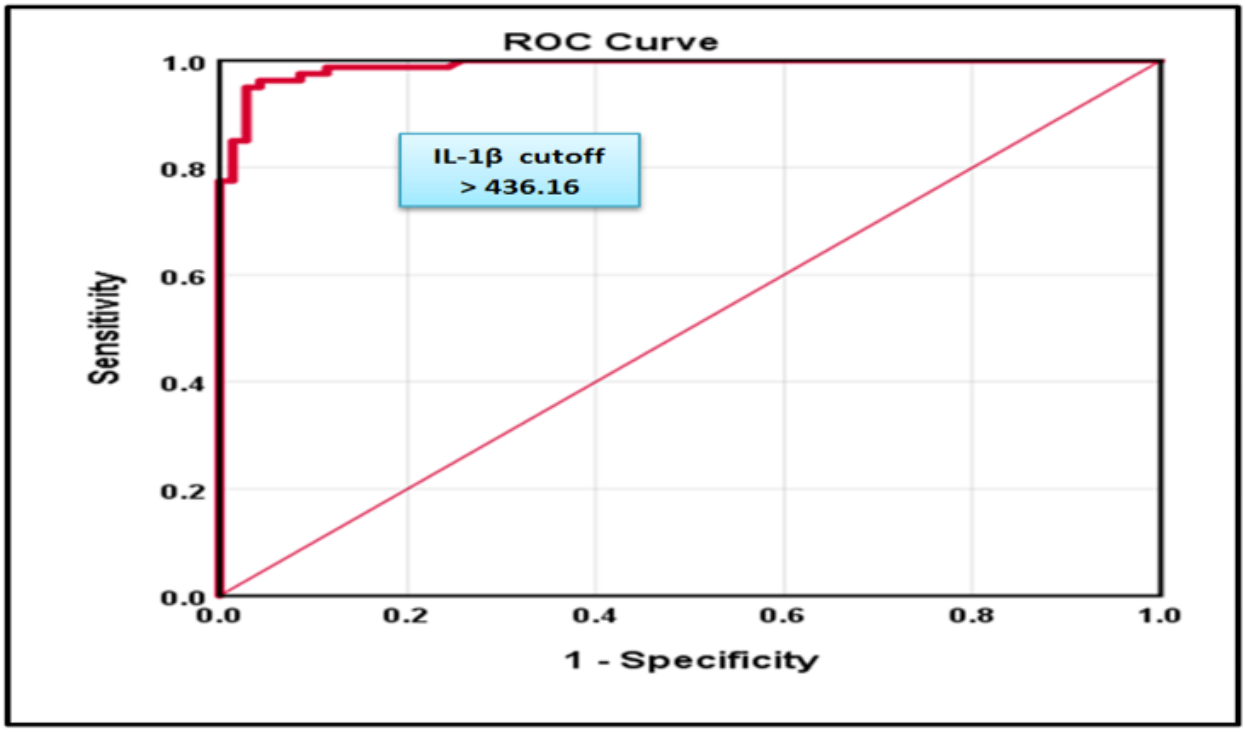


**Figure 4.** *Receiver operator s characteristic s curve analysis of IL-1β for the determination of possible diagnostic s cutoff value*

**Evaluation of I risin**

To determine the Irisin cutoff value and anticipate the gout disease as Receiver operator characteristic (ROC) curve analysis was done to determine whether the tests were diagnostic or adjuvant diagnostic tests. The outcomes are displayed in Table (7) and Figure(5). The Irisin cutoff value was greater than 13.05-fold and specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), and area under curve values of 98.8%, 98.6%, 98.8%, and 0.999 (0.996-1.000).

| Irisin level | Gout patients n = 80 | Healthy control n = 70 |
|---|---|---|
| >13.05 | 79 (%) | 1 (%) |
| < 13.05 | 1 (%) | 69 (%) |
| Sensitivity % | 98.8 % | |
| Specificity % | 98.6% | |
| PPV % | 98.8% | |
| NPV % | 98.6% | |

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| | |
|---|---|
| AUC (95% CI) | 0.999 (0.996- 1.000) |

**Table 7.** *Sensitivity and specificity of Irisin level > (13.05 fold ) in gout disease*

CI is for confidence interval, while AUC stands for area under curve.

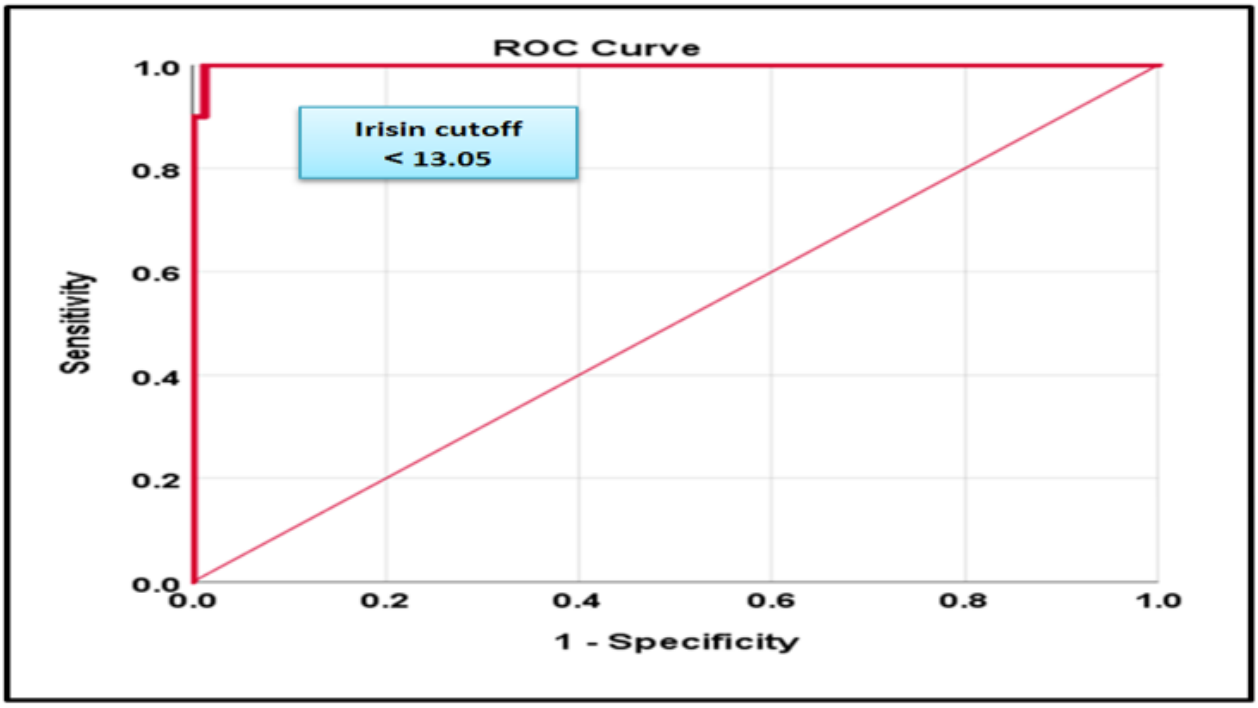


**Figure 5.** *Receiver operators characteristics curve analysis of Irisin for the determination of possible diagnostics cutoff value*

Gout arthritis has two characteristics, involving the inflammasome's activation and the MSU-induced generation of mature IL-1β[5]. The NLRP3 inflammasome requires activation by two separate signals in order to create mature IL-1β[18]. The initial signal that sets off the activation of the NLRP3 inflammasome is still unknown. When considering the mechanism behind uric acid-induced gouty inflammation, it is vital to understand how other pro-inflammatory chemicals recognize MSU-mediated inflammasome activation and IL-1β[19]. In addition to IL-1β, GA is a condition characterized by inflammation where urate crystals result in the activation of white blood cells[20].

The examination of serum Interleukin-1 concentrations in gout patients and healthy controls is provided in Table (3) and Figure (2) as research findings. The level was substantially greater in the "patients group" as comparison to the healthy control (P 0.001), and the mean serum IL-1 levels were 781.88 314.45 pg/ml and 316.79 94.85 pg/ml, respectively, in gouty patients and healthy controls.

The findings of this study concur with those of Martinon et al, who demonstrated that monosodium urate crystals activated caspase-1, which in turn caused NALP3 to become active and increased levels of active interleukin IL-1β[9].

The pathophysiology for gouty inflammation is associated with a growing and activation the NLRP3 inflammasome, which is a protein that contains the LRR, NOD, and pyrin domains. This inflammasome then produces proinflammatory cytokines.

It is cannot to ascribe the stimulation of inflammasome component assembly and expression to MSU crystals alone. Preparing macrophages produced from monocytes is the earliest sign of gouty inflammation. The second signal, which is brought on by MSU crystals, causes multiprotein intracellular inflammasomes of NLRP3 to form, which include pro-caspase 1. Then, to make the active versions, active caspase 1 cleaves molecules like IL-1β and other precursors. When IL-1β is released, neutrophils are drawn to the area of inflammation, more pro-inflammatory cytokines are produced, and cartilage and bone are degraded[21].

In addition, the irisin was first recognized In 2012, Bostrom postulated that skeletal muscle secretes this hormone in response to exercise[22]. Functional studies have shown that irisin is easily measurable in serum and may circulate through white adipose tissue, which may cause a transition from white within brown-like adipose tissue because brown adipose tissue is skilled at releasing energy by creating heat[23]. Irisin is very useful for treating

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several metabolic illnesses, including diabetes, nonalcoholic fatty liver, metabolic syndrome, and obesity[24][25][26]. Myokine and AMP-activated protein kinase (AMPK), two important metabolic regulators, are also activated by exercise. Additionally, PGC1-a can be directly phosphorylated by AMPK[27], activating FNDC5 and increasing serum irisin levels. Irisin controls chondrocyte proliferation and mortality while preserving the extra chondral matrix's integrity, which can have a direct impact on the development of osteoarthritis. The extracellular matrix degrades and chondrocytes die as a result of the osteoarthritis (OA) inflammatory process[28].

In this study, the usefulness of serum irisin, a novel potentially protein biomarker, as a predictor of gout activity, was investigated in relation to other parameters in Figure(3) and Table (4), Mean levels of serum Irisin were 6.76 ± 2.91 ng/ml and 17.03 ± 4.14 ng/ml, in gouty patients and healthy control respectively; and the level was highly significantly lower than in "patients group" in comparison with healthy control ($P < 0.001$).

We contrasted gout, a severe type of arthritis, to osteoarthritis, where early studies on the association between the irisin levels and the condition employed serum samples from individuals with knee discomfort. There was shown to be a negative connection between serum irisin concentration and the severity of osteoarthritis when those levels dropped[29][30].This study is also in accordance with research on the effects of irisin on the skeleton, which revealed a link between vertebral fragility fractures and low irisin levels in postmenopausal women. Yet, in athletes, The concentrations were directly correlated with bone mass and density, demonstrating irisin's preventative function in bone health[31]. But nonetheless, the central nervous system is also affected by the irisin action. Irisin received interest due to its potential use in treating neurodegenerative illnesses like Alzheimer's and Parkinson's[32][33].

Several variables, body mass index (BMI), including gender, muscle mass, age, and training, have an impact on irisin serum levels[34]. Also, the findings of the Pearson correlation study revealed that irisin and IL- 1β have a negative association, where R (-0.080), p (0.481). Irisin is negatively correlation with Uric Acid where

R ( -0.023),p (0.842). As well as The correlation was positive between IL-1β and Uric Acid where R (0.101 ), p (0.895)as shown in Table (5).

Also, the ROC curve analysis findings were displayed in Tables (6). (7) and Figure (4), (5) that the AUC(95%CI) for serum IL-1β and irisin was 0.990(0.979-1.000) , 0.999(0.996-1.000) respectively, Both serum IL-1β and irisin are the preferred biomarkers for the diagnosis of gout, and it has been demonstrated that both are useful in distinguishing gout patients from healthy volunteers.

# Conclusion

The combination of the cytokine that causes inflammation (IL-1), the myokine (irisin), and blood uric acid may improve the accuracy of gout diagnosis, as this study is the first to show It is clear that multicentric trials are required to verify this combination's efficacy in gout diagnosis.

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