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Investigating Role of IL-39, IL-37 and Some Biochemical Parameters in Patients with Acute Interstitial Nephritis

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Abstract. Background: Acute interstitial nephritis causes blood flow to be impaired, this ultimately leads to inflammation and edema in the renal tubules and tissues, this decreases the glomerular filtration rate (GFR). Early detection and treatment of the disease can mitigate the progression of renal failure. To investigate the potential for IL-39 and IL-37 to be used in the diagnosis of acute interstitial nephritis, this study sought to measure the levels ofinflammatory markers, interstitial nephritis, and antioxidant agents in patients with acute interstitial nephritis using receiver operating characteristic (ROC) graphs.Methods: The investigation had 25 patients and 25 controls that were between the ages of 40 and 65 during the years 2023 and 2024.Results: The outcomes demonstrated that the concentrations of urea, creatinine, C-reactive protein (CRP), IL-39, IL-37, and MDA in the patient's blood were significantly greater than those in the control's. However, the concentrations of albumin, GSH, and SOD in the blood of the patients were significantly lower than those of the controls. Additionally, the ROC curve demonstrated that the concentrations of MDA,TNF-α,GSH,SOD,IL-39, and IL-37 were effective at differentiating patients with acute tubular necrosis from healthy individuals. Overall, inflammation has been linked to increased oxidative stress, the release of proinflammatory cytokines, and the development of an inflammation state. As a result, understanding the total disease burden and adding extra criteria will facilitate the early detection or preemptive risk assessment for each patient. This will facilitate future investigations of the pathophysiology of diseases in diagnosis, prognosis, and treatment.

Highlights:

1. IL-39 and IL-37 show strong diagnostic potential for acute interstitial nephritis.
2. Patients exhibited higher inflammation and oxidative stress markers, with reduced antioxidant levels.
3. ROC analysis confirmed several biomarkers as effective differentiators from healthy controls.

Keywords: Acute Interstitial Nephritis, IL-39, IL-37, Oxidative Stress, ROC Curve

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Introduction

Based on the underlying aetiology, duration of the illness, and tissue biology, acute and chronic interstitial nephritis may be differentiated [1]. Acute interstitial nephritis (AIN) affects 10% to 20% of individuals with acute kidney injury (AKI) who have a renal biopsy. Because persistent inflammation causes kidney damage, including fibrosis, loss of renal function may be lessened if it is identified and treated quickly. Between 40 and 60 percent of individuals may get chronic renal damage after an incident of AKI [2]. AKI of any cause is seen in 1% to 3% of renal biopsies performed worldwide. The general incidence of AKI rises to 15% to 27% when research is restricted to individuals with AKI [3,4]. While viral and autoimmune disorders are less frequent in wealthy nations, infectious causes of AKI are more prevalent in less developed nations. Due to a compromised immune system and increasing pharmaceutical usage, drug-induced AKI is more prevalent in older adults than systemic or autoimmune disorders [1]. The tubulointerstitial tissue is vulnerable to damage because of its high metabolic needs and inadequate blood supply [5]. Inflammation and swelling of the tubules and surrounding tissues are hallmarks of interstitial nephritis, which lowers blood flow and eventually affects the glomerular filtration rate (GFR). In later stages, the illness may have substantial repercussions even if it damages the glomeruli less [6–8]. Collagen and extracellular matrix are produced as a result of the production and activation of cytokines in interstitial nephritis. This stops the buildup of collagenases and metalloproteinases, which cause fibrosis. Interstitial nephritis raises angiotensin II activity, which raises blood pressure, since it supplies cells with fluid and salts. Moreover, it causes oxidative stress and decreases vasodilation. According to some research, the production of ROS brought on by oxidative stress may worsen mitochondrial damage, which can result in the release of cytochrome c and other elements linked to apoptosis into the cytoplasm [5]. Interleukins may enhance renal vascular porosity, which directly affects renal cells and causes an inflow of inflammatory cells, since they upregulate the production of adhesion molecules. Thus, knowing how interleukins contribute to renal inflammation might aid in the creation of a possible remedy. Inflammation may be decreased and renal function preserved by focussing on certain interleukins. In order to assess the effectiveness of biomarkers and their correlation with acute interstitial nephritis, this

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studies looked at the blood stages of IL-39 and IL-35 in individuals with the circumstance. Furthermore, the affiliation among oxidant and antioxidant ranges and IL-37 and IL-39 become investigated, and a receiver running feature (ROC) curve became used to observe the predictive fee of interleukin 39 in acute interstitial nephritis.

Materials and Methods

A. Samples Collection and Laboratory Tests

Fifty participants were involved in the study, including 25 patients and 25 controls. The sample size was determined using the Stephen Thompson formula. Patients who registered at Al-Hussein Teaching Hospital, Dhi Qar Governorate from 2023 to 2024 were assigned by randomization. The patients' ages in the acute form of interstitial nephritis were between 40 and 65, while controls had a similar age composition. We gathered 25 patients that had medical records that were biopsy-validated. Six patients (24%) had diseases that affected the entire system, including two cases of IgG-related disease and four cases of Systemic lupus erythematosus. Five patients (20%) had diseases that were caused by infectious agents, and 10 patients (40%) had diseases that were caused by drugs, the majority of which were antibiotics or non-steroidal anti-inflammatory drugs. Four subjects (16%) were labeled as having primary AIN. Five milliliters of blood were gathered from each participant (controls and patients). Insert the sample into a vacant container, let it remain at a temperature that's appropriate, and then centrifug it at 3000 × g for 10 minutes. If the serum is not utilized immediately, it should be stored at - 20°C for the subsequent measurement of chemical properties. Measuring the concentrations of TNF-A, MDA, CRP, GSH, and other common laboratory components like albumin, creatinine, and ornamental plants. ELISA-based immunosorbent assays (ISAs) were used to determine the levels of TNF-A, CRP, IL-39, and IL-37 in the blood.

B. Statistical Analysis

The mean ± SD) is used to display experimental results. When comparing parameters with more than two analysis groups, the t-Test will be used. At $P < 0.05$, it will be deemed statistically significant. Relationships between different parameters within each patient group will be described using Pearson correlation

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coefficients (r). Analysis of Receiver Operating Characteristics (ROC) will also be carried out.

Result and Discussion

In this study, 50 cases were divided into two groups: 25 patients and 25 healthy individuals. There was no significant difference in the age of the two groups. Table 1 describes the specific attributes of the two classes in detail.

Table 1. Information on the age and sex of the groups under study

Groups	No.	Age (years)	BMI (Kg/m^2)	Sex (M/F)
Controls	25	50.12± 5.34	24.34±3.48	10/15
Patients	25	56.34± 6.45	26.43±5.34	11/14

No: Number, M: male , F: Female , BMI: body max indexes

The criteria for clinical examinations of the kidneys are listed in Table 2. The table demonstrates that the blood urea and creatinine levels in the patient group were significantly greater than those in the control group. However, the same information also demonstrated that the serum albumin content in the patient group was significantly lower than that in the control group. The same findings demonstrated that the CRP level in the patient's blood was also significantly greater than that in the control group.

Table 2. The levels of serum urea, creatinine, albumin, and CRP in patients and controls are described.

Groups	Controls Mean ±SD	Patients Mean ±SD	P-value
Urea mg/dL	26.25 ± 4.21	62.34 ± 6.78	0.004
Creatinine mg/dL	2.67 ± 0.69	0.69 ± 0.12	0.000
Albumin g/dL	4.96 ± 0.87	3.42 ± 1.03	0.009
CRP mg/L	6.79± 0.85	32.19 ± 3.45	0.002

The concentrations of tumor necrosis factor-α, interleukin-39, and interleukin-37 in patients and the control group are listed in Table 3. The data in the table indicates that the serum levels of IL-39, IL-37, and TNF-α in the patient group were significantly greater than those in the control group.

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Table 3. The serum concentrations of TNF-α, IL-39, and IL-37 in patients and controls.

Groups	Controls Mean ±SD	Patients Mean ±SD	P-value
IL-39 ng/L	8.47±1.08	± 3.2021.78	0.000
IL-37 pg/mL	18.35±2.14	75.21± 7.23	0.000
TNF-α pg/mL	2.64±0.58	4.86±0.84	0.005

Table 4 demonstrates that the serum MDA level in the patient group was significantly greater than that in the control group. However, the same table also demonstrates that the blood GSH and SOD levels in the patient group were significantly lower than those in the control group.

Table 4. The serum levels of MDA, GSH, and SOD in patients and controls.

Groups	Controls Mean ±SD	Patients Mean ±SD	P-value
MDA µmol/L	1.32±0.21	±0.793.58	0.001
GSH Ug/mL	3.01±0 .51	1.89±0.23	0.000
SOD ng/mL	4.85±0.93	2.31±0.49	0.000

In clinical epidemiology, the ROC method is employed to assess the capacity of medical diagnostic procedures to differentiate between infected and uninfected patients. The idea behind it is a scale in C that calculates the results of two conditions in succession. One important indicator of the reliability of a diagnostic test regarding sensitivity and accuracy is the area under the curve (AUC). In this research, the ROC curve was employed to assess the results of the test and the investigation. Table (5) provides specific information. If the test's result is greater than the table's value (0.5), all of the evaluation indicators have some degree of significance in predicting acute interstitial nephritis. Also, the final conclusion that the AUC arrives at is of great importance. The ROC curve demonstrates that the level of IL-39 is extremely effective in differentiating between individuals with the greatest health and patients with acute renal failure. As a result, it's legitimate to believe that IL-39 is undoubtedly involved

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in thegnosis of acute tubular nephritis. TNF and IL-37 have been demonstrated to differentiate between patients with acute renal failure and healthy individuals. However, MDA, GSH and SOD are also significant components.

Table 5. The total area under the ROC for each biomarker studied

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
IL-39 ng/L	0.945	0.004	0.001	0.835	0.922
IL-37 pg/mL	0.810	0.035	0.015	0.729	0.867
TNF-α pg/mL	0.839	0.038	0.039	0.837	0.928
MDA µmol/L	0.743	0.061	0.033	0.767	0.928
GSH Ug/mL	0.786	0.074	0.029	0.686	0.868
SOD ng/mL	0.754	0.068	0.018	0.732	0.834

Pearson's correlation explained the association between IL-39 and other variables in this investigation. Table 6 demonstrates that IL-39 was positively associated with (urea, creatinine, CRP, IL-37, TNF-α, and MDA). IL-39 was associated with (albumin, GSH, and SOD) negatively.

Table 6. The association between IL-39 and other variables.

IL-39 with	r	p-value	Result
Urea mg/dL	0.43	0.005	Significant positive correlation
Creatinine mg/dL	0.52	0.000	Significant positive correlation

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Albumin g/dL	- 0.31	0.087	Insignificant negative correlation
CRP mg/L	0.57	0.032	Significant positive correlation
IL-37 pg/mL	0.44	0.011	Significant positive correlation
TNF-α pg/mL	0.41	0.026	Significant positive correlation
MDA µmol/L	0.45	0.009	Significant positive correlation
GSH Ug/mL	- 0.39	0.062	Insignificant negative correlation
SOD ng/mL	- 0.56	0.002	significant negative correlation

Inflammation and oedema of the tubules and interstitial tissue are hallmarks of interstitial nephritis, which lowers blood flow and, eventually, glomerular filtration rate (GFR). Typically, the glomeruli are unaffected and only subsequently impacted. The severity of renal failure may be lessened if it is identified and treated quickly since ongoing inflammation can cause kidney damage, including fibrosis. Furthermore, inflammatory activity may be assessed by regular inflammatory markers and normal renal function testing. In this research, individuals with acute interstitial nephritis had their levels of oxidative-antioxidant, interleukin, and inflammatory markers evaluated. Interleukin levels in the human body may be used to identify a wide range of illnesses that impact contemporary society, such as cancer [9–11], heart disease [12–14], neurological disorders [15,16], and renal disease [17–19]. Since these interactions may have negative health repercussions, more thorough scientific and clinical study is required to examine the biological functions of interleukins and their interactions with other body cells. Numerous immunological and non-immune cells create low molecular weight glycoproteins called cytokines. Through autocrine, paracrine, and endocrine processes, they are released into the bloodstream and regulate several facets of the inflammatory and immunological response [20–22]. One of the main characteristics of renal illness is inflammation. Local immune cells such dendritic cells, macrophages, and circulating monocytes, lymphocytes, and neutrophils often develop intricate associations with renal parenchymal cells [23]. Inflammatory mediators, such as acute phase proteins, chemokines, and cytokines, may cause permanent tissue damage and loss of function, metabolic reprogramming, and phenotypic alterations in inflammatory,

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immunological, and tissue cells [24]. By stimulating all innate immune pathways and pattern recognition receptors (PRRs), these cells become activated. According to studies, afflicted groups had far greater levels of IL-39 and IL-37 than controls. According to earlier research, IL-39 is a dimeric heteroglycoprotein made up of the IL-23p19 and Ebi3 subunits that are covalently bonded. Although the immunological role of IL-39 is still unclear, research in animal models that resemble lupus has shown that the proinflammatory effects of IL-39 most likely contribute to the pathogenic immune pathways of systemic lupus erythematosus (SLE) [25]. Acute coronary syndrome patients had significantly higher blood levels of IL-39, and the authors said that "IL-39 can be considered an indicator of contractile dysfunction" [26]. Autoimmune inflammatory demyelinating disorders such visual neuropathy have been linked to elevated IL-39 levels [27]. Concanavalin A-induced hepatitis may be made worse by IL-39, according to studies [28]. According to this research, IL-39 could be involved in the aetiology of inflammatory disorders in humans. Consequently, it is hypothesised that IL-39 is a necessary cytokine whose pathogenic role requires further research. This study's primary goal was to investigate IL-39's suitability as an AIN biomarker. The use of IL-39 in AIN is supported by the ROC curve study findings (AUC = 0.973). Thus, the findings of the study suggest that IL -39 may be a different goal for auxiliary IN Diagnostic marker and/or alternative disease therapy. IL-37, one of the other interleukin checked, was much higher in the patient's group compared to the control group. Due to its anti -inflammatory qualities and the ability to support the immune system as cytokine, interleukines 39 and 37 were selected for this investigation. By suppressing immune reactions and acting as an anti -inflammatory agent, IL -37 can help keep inflammatory pro and anti -inflammatory systems in balance [29]. In this investigation, the elevated tumor necrosis factor (TNF-α) levels were also found. Renal tubular epithelial cells use numerous cell types, including dendritic cells and macrophages, powerful regulator of inflammatory reactions, tumor necrosis factors (TNF).TNF-α primarily activates three pathways: mitogen-activated protein kinases (MAPKs), caspases, and nuclear factor κB (NF-κB). Secondary reactions are triggered by the NF-κB and MAPK signalling pathways, which raise the levels of many proinflammatory cytokines. Consequently, TNF-α14 production is triggered. Furthermore, elevated blood levels of TNF-α are clearly associated with the degree of kidney injury [30]. Oxidative

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stress may be a byproduct of inflammation, and it can worsen inflammation by triggering many signalling pathways. An overabundance of reactive oxygen species (ROS) and an imbalance between oxidants and antioxidants are characteristics of the oxidative system [31, 32]. Elevated oxidative stress improves cellular resistance to structural damage and raises the risk of tissue damage. Since oxidative stress may be brought on by TLR and inflammasome signalling pathways, immune inflammation and oxidative stress are tightly connected. In fact, immunological inflammation may lead to an autotoxic loop by boosting the generation of ROS and RNS. ROS are produced by activated microglia and worsen the local inflammation until they are eliminated by necrosis, apoptosis, or cell death. Because it raises oxidative stress and generates proinflammatory cytokines, inflammation is regarded as the first stage of the inflammatory state. Since all of these processes contribute to the development of illness, controlling them may help accomplish this aim and lower the probability of following aetiologies [33].

Conclusions

It is possible to state that inflammation causes oxidative stress, the production of pro-inflammatory cytokines, and the development of aninflammatory state. Since each of these systems is involved in the development of the disease, controlling them will help to reduce the future risk factors associated with development of the disease. As a result, understanding the total disease burden and adding extra criteria will facilitate the early detection or preemptive risk assessment for each patient. This will facilitate future studies that explore the pathophysiology of diseases in regards to diagnosis, prognosis, and treatment.

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