Am J Transl Res 2022;14(5):3189-3197
www.ajtr.org /ISSN:1943-8141/AJTR0138411

Original Article

Serum IL-6 as a marker of disease progression in interstitial nephritis

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Received August 19, 2021; Accepted January 20, 2022; Epub May 15, 2022; Published May 30, 2022

Abstract: Objective: To investigate the mechanism of serum interleukin-6 (IL-6) change in disease progression of interstitial nephritis. Methods: This is a retrospective study. From November 2017 to November 2019, 87 patients with interstitial nephritis treated in our hospital were enrolled and divided into an acute group (n=42) and a chronic group (n=45) based on pathological results of renal biopsies. Forty healthy individuals after physical examination during the same period were enrolled into the reference group. Serum IL-6 levels were determined using the enzyme-linked immunosorbent assay (ELISA). Results: Among the three groups, patients in the acute group showed the highest IL-6 level (P<0.001). The acute group obtained higher serum advanced oxidation protein products (AOPP) levels and glomerular filtration rate (GFR) than the other two groups (P<0.05). The acute group showed lower levels of $CD34^+$ [number of positive microvessels (MVs)/HP], a smaller type III collagen positive area, and a larger type IV collagen positive area than the chronic group (P<0.05). The acute group obtained higher levels of IL-27 and tumor necrosis factor-α (TNF-α) than the chronic group (P<0.001). The acute group had higher levels of serum creatinine (SCr), erythrocyte sedimentation rate (ESR), estimated glomerular filtration rate (eGFR), and 24-hour urine protein quantity (24 h UPQ) than the other groups (P<0.001). The combined detection of serum IL-6, TNF-α, and microalbumin (mALB) outperformed the stand-alone approach (P<0.05). Serum IL-32 and kidney injury molecule-1 (KIM-1) levels in the acute and chronic group were positively correlated with SCr and 24 h UPQ (P<0.05). Conclusions: Serum IL-6 shows a great potential as an important marker of disease progression in interstitial nephritis.

Keywords: Serum IL-6, interstitial nephritis, progression markers, mechanism

Introduction

Interstitial nephritis, also known as tubulointerstitial nephritis, is a group of kidney diseases triggered by different etiologies with interstitial inflammation of the kidney as the main lesion [1, 2]. The clinical symptoms include nocturia, polyuria, muscle weakness, and arthralgia, which have impact on most of the renal tubules, thereby impairing urinary function. Current evidence suggests that increased levels of inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are crucial in the progression of kidney diseases [3]. It has been suggested [4] that chronic inflammation and the activation of the immune system are the leading causes of interstitial nephritis, which are also accompanied by the accumulation of inflammatory cytokines such as macrophage and T cells during the development of the disease. Moreover, the degree of accumulation of inflammatory cells and cytokines is closely related to the progression of interstitial nephritis, which can directly damage the structure of patients' kidneys and promote the transformation of epithelium to mesenchyme, resulting in extracellular matrix accumulation, and aggravating the impairment and inflammatory response of the kidneys [5]. Inhibition of the release of inflammatory factors may help alleviate interstitial nephritis. Therefore, inflammation is considered a key pathogenic factor for the occurrence and progression of interstitial nephritis [5, 6]. IL-6, a lymphokine produced by activated T cells and fibroblasts, is crucial in the body's anti-infective immune response as

it promotes the growth and differentiation of primitive osteogenic cells and enhances the lytic function of natural killer cells [7, 8].

Research has shown that the incidence of interstitial nephritis among adults over 30 years of age is about 6.5%, with a gradual rise in recent years [9-11]. The symptoms of the disease at its early stage are rather hidden and lack of specificity, which predisposes to an omission of the disease until the appearance of apparent symptoms such as proteinuria and hematuria caused by kidney toxin accumulation, resulting in delayed diagnosis, missed optimal timing for treatment, and poor prognosis [12-14]. Studies have confirmed that infection remains the leading cause of interstitial nephritis, with pathogens including bacteria, fungi, and viruses. Heavy metal contamination and metabolic abnormality are also involved in its pathogenesis. It was found that the expression of inflammatory mediators and cytokines triggered by cellular immunity and humoral immunity causes a cascade of biochemical reactions that ultimately result in renal injury [15].

Currently, the most intensively studied inflammatory mediators and cytokines include anti-inflammatory factors, pro-inflammatory factors, and adhesion factors, such as TNF-α and IL-6 [16-18], among which IL-6 causes the abnormal proliferation of glomerular mesangial cells leading to interstitial diseases, generates extracellular matrix deposits in glomeruli and renal interstitium, induces endothelial cytotoxicity, and promotes inflammatory cell infiltration, which ultimately gives rise to the loss of immune function of kidney tissue and the deterioration of renal function. TNF-α also promotes abnormal proliferation of endothelial cells, epithelial cells, and other intrinsic renal cells, which induces the expression of inflammatory factors and injury to interstitial cells [19, 20]. During the progression of renal interstitial fibrosis, TNF-α exacerbates glomerulosclerosis through its fibrogenic features and effects on hemodynamic instability. Therefore, TNF-α can serve as an important serum marker to evaluate renal function deterioration in patients with interstitial nephritis [21, 22].

Therefore, this study was to investigate the mechanism of IL-6 as a marker of disease progression in interstitial nephritis and to provide new options for clinical practice. The novelty of this study lies in the detection of inflammatory markers of disease with the aim of providing a drug target.

Materials and methods

From November 2017 to November 2019, 87 patients with interstitial nephritis treated in our hospital were retrospectively enrolled and divided into an acute group (n=42) and a chronic group (n=45) based on the pathology of the renal biopsies. Another 40 healthy individuals after physical examination were assigned to the reference group.

Inclusion criteria

(1) Patients who were pathologically confirmed as interstitial nephritis by renal biopsies; (2) Patients with clinical manifestations mainly including proteinuria, swelling, and renal insufficiency; (3) Patients with inflammatory infiltrates in the interstitium of normal glomeruli and small renal vessels; (4) Reference subjects without a history of kidney disease; (5) Patients with no recent use of medications.

Exclusion criteria

(1) Patients who had been diagnosed with secondary or primary glomerular diseases; (2) Patients with recurrent episodes of sarcoid hematuria; (3) Patients with renal biopsy results showing glomerular thylakoid cells and stromal hyperplasia as indicated by light microscopic examination and IgA-based immune complex deposition in the glomerular thylakoid region as indicated by immunofluorescence; (4) Patients with other systemic diseases, cystic nephritis, or urinary tract infection; (5) Patients with pregnancy or a history of cancer.

This study was approved by the hospital ethics committee, with ethics approval number of 2017-10-24, and all participants signed an informed consent form before enrollment in this study.

Methods

Fasting elbow venous blood was collected from all participants in the early morning and centri-

Table 1. Comparison of clinical information among 3 groups

Groups	Acute Group (n=42)	Chronic Group (n=45)	Reference Group (n=40)	χ^2/F	*P*-value
Gender				0.318	0.573
Male	24 (57.14%)	23 (51.11%)	21 (52.50%)		
Female	18 (42.86%)	22 (48.89%)	19 (47.50%)		
Mean Age (years)	41.26±2.76	41.31±2.65	41.27±2.59	0.058	0.954
Weight (kg)	70.35±5.41	70.37±5.38	70.42±5.43	0.039	0.969
BMI (kg/m^2)	21.32±1.22	21.36±1.25	21.29±1.32	0.170	0.866
Residence				0.024	0.878
Urban	20 (47.62%)	21 (46.67%)	18 (45.00%)		
Rural	22 (52.38%)	24 (53.33%)	22 (55.00%)		

fuged to obtain the supernatant which was then stored at -80°C. Serum IL-6, IL-27, Il-32, and TNF-α levels in the blood samples were determined using an ELISA kit (kt. 178013, Shanghai Zhenke Biotechnology, China) according to the kit instructions. The specific steps were described previously [9, 10].

Serum advanced oxidation protein products (AOPP) levels of the three groups of subjects were determined using the UV spectrophotometric method, and the spectral characteristics were analyzed using high-performance gel chromatography. The glomerular filtration rates (GFRs) were also calculated.

Definiens Tissue Studio Digital Pathology Image Analysis Software was used to calculate the percentage of α-smooth muscle actin (α-SMA)-positive and the positive area of type IV and type III collagens. The number of CD34$^+$ microvessels (MVs) was determined to reflect the level of capillaries around the renal tubules. The kidney tissue samples of the patients in the acute group and the chronic group were collected by pathological kidney tissue biopsy, and the kidney tissue samples of the patients in the reference group were collected by tissue biopsy after a physical examination suspicious of interstitial nephritis.

For both acute and chronic groups, 8 mL morning urine was collected and centrifuged (Hunan Hengnuo Instrument Equipment Co., Ltd, China) at 3000 r/min for 15 minutes to collect the supernatant. An automatic biochemical analyzer (Mindray Biotechnology Co., Ltd, China) and the kit (kt. 178016 Shanghai Zhenke Biotechnology, China) were used to determine the level of micro-albumin (mALB). Serum creatinine (SCr, kt. 178266 Shanghai Zhenke Biotechnology, China), kidney injury molecule-1 (KIM-1, kt. 178281, Shanghai Zhenke Biotechnology, China), and erythrocyte sedimentation rate (ESR, kt. 178219, Shanghai Zhenke Biotechnology, China) of the three groups were determined using an automatic biochemical analyzer. The 24-hour urine protein quantity (24 h UPQ) of the three groups was measured using immune turbidimetry. Estimated glomerular filtration rate (eGFR) = 1.86 × SCr-1.154 × Age-1.154 (0.742 in female) × 1.233.

Statistical processing

All data in this study were analyzed using SPSS 21.0 and visualized to graphics by GraphPad Prism 7 (GraphPad Software, San Diego, USA). The measurement data ware expressed as ($\bar{x}$ ±sd). One-way ANOVA was used for comparison among multiple groups, and LSD-t test was used for further pairwise comparison. The counting data were expressed as [n (%)] and analyzed using the chi-square test. A *P*-value less than 0.05 indicated a statistically significant difference.

Results

Comparison of clinical information

The three groups of patients showed no significant difference in gender, age, weight, BMI, and place of residence (**Table 1**).

Serum IL-6

The levels of IL-6 in acute, chronic and reference groups were 139.63±7.43 pg/mL,

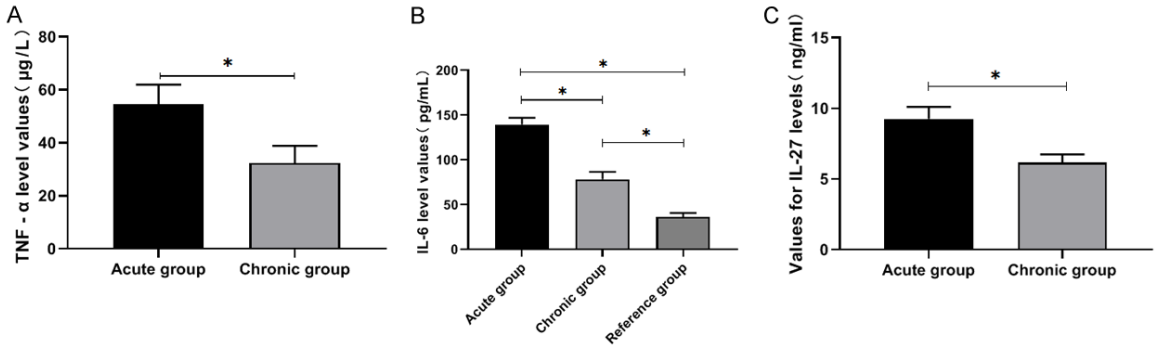

Figure 1. Comparison of IL-6, IL-27 and TNF-α Level ($\bar{x}$±sd). Note: A. The abscissa indicates acute and chronic groups from left to right, and the ordinate indicates the TNF-α level in μg/mL. There was a significant difference in TNF-α level between the acute group and the chronic group (t=14.979, *P<0.05). B. IL-6 levels in the acute group, the chronic group and reference group. There was a significant difference in IL-6 level between the acute group and the chronic group (t=40.691, *P<0.05), between the acute group and the reference group (t=76.264, *P<0.05), and between the chronic group and the reference group (t=28.557, *P<0.05). C. The abscissa indicates acute and chronic groups from left to right, and the ordinate indicates the IL-27 level, ng/mL. There was a significant difference in IL-27 level between the acute group and the chronic group (t=19.766, *P<0.05).

Table 2. Comparison of serum AOPP and GFR among 3 groups ($\bar{x}$±sd)

Groups	n	AOPP (μmol/L)	GFR (mL/min)
Acute Group	42	91.24±14.63	38.42±2.35
Chronic Group	45	56.72±9.83	33.63±2.16
Reference Group	40	38.74±7.82#,*	30.34±2.45#,*
F		23.654	12.456
P		<0.01	<0.01

Note: AOPP: advanced oxidation protein products; GFR: glomerular filtration rate; #represents the comparison between the acute group and the reference group, *represents the comparison between the chronic group and the reference group, P<0.05.

78.45±8.36 pg/mL, and 36.37±4.36 pg/mL, respectively. Patients in the acute group had the highest IL-6 level, followed by the reference group (P<0.001; **Figure 1B**).

Comparison of serum AOPP and GFR

Significantly higher levels of serum AOPP and GFR were observed in the acute group compared with the chronic group and the reference group (P<0.05), and the chronic group had higher AOPP and GFR levels than the reference group (P<0.05; **Table 2**).

Comparison of renal interstitial MVs and fibrosis indicators

A lower level of $CD34^+$ (number of positive MVs/HP) and a smaller type III collagen positive area were obtained in the acute group than those in the chronic group (P<0.05), while type IV collagen positive area in the acute group was significantly larger than that in the chronic group (P<0.05). There was no significant difference in α-SMA-positive rate between the acute group and chronic group (P>0.05; **Table 3**).

Comparison of IL-27 and TNF-α levels

The average levels of IL-27 in the acute and chronic groups were 9.25±0.86 ng/mL and 6.16±0.58 ng/mL, respectively. The average levels of TNF-α in acute and chronic groups were 54.62±7.34 μg/L and 32.34±6.53 μg/L, respectively. The IL-27 and TNF-α levels in the acute group were higher than those in the chronic group (P<0.001; **Figure 1A**, **1C**).

Correlation analysis of serum IL-6 and TNF-α

A significant correlation between serum IL-6 and TNF-α was detected in patients with interstitial nephritis (P<0.001; **Figure 2**).

Comparison of SCR, ESR, eGFR, and 24 h UPQ

Compared with the chronic group and the control group, the eGFR level in the acute group was significantly decreased, while the levels of SCr, ESR and 24 h UPQ were significantly increased (P<0.001; **Table 4**; **Figure 3**).

Table 3. Comparison of renal interstitial MVs and fibrosis indexes between acute and chronic groups ($\bar{x}$±sd)

Groups	n	$CD34^+$ (number of positive MVs/HP)	α-SMA-positive rate (%)	Type III collagen positive area (%)	Type IV collagen positive area (%)
Acute Group	42	22.64±3.25	0.09±0.03	0.03±0.01	0.10±0.02
Chronic Group	45	28.73±3.68	0.07±0.01	0.08±0.02	0.05±0.01
t		8.158	4.229	14.585	14.898
P		<0.01	<0.01	<0.01	<0.01

Note: MVs: microvessels; α-SMA-positive: α-smooth muscle actin-positive.

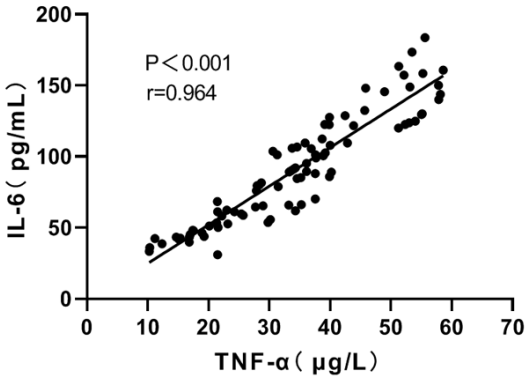

Figure 2. Correlation analysis of IL-6 and TNF-α. Note: a total of 87 cases were included for analysis.

Comparison of diagnostic value of single and combined detection of serum IL-6, TNF-α, and mALB

The combination of serum IL-6, TNF-α, and mALB yielded higher diagnostic AUC value, sensitivity, and specificity than each single approach (P<0.05; **Table 5**).

Pearson correlations of IL-32 and KIM-1 with SCR and 24-h UPQ

Serum IL-32 and KIM-1 levels in acute and chronic groups were positively correlated with SCr and 24 h UPQ (all P<0.05; **Table 6**).

Comparison of organ function based on high or low TNF-α and IL-6 levels

The expression levels of Cr, BUN, $AaDO_2$, and PaO_2/FiO_2 differed significantly among patients with high or low TNF-α and IL-6 expression levels (P<0.001; **Table 7**).

Discussion

The early clinical manifestations of acute interstitial nephritis include fever, swollen lymph nodes, and skin rash. Clinically, glucocorticoid therapy is frequently used for patients with acute interstitial nephritis. It prevents further renal deterioration and enhances renal function, but also impairs the patients' immunity, which may aggravate renal function impairment in case of improper control [6]. IL-6 is a lymphokine synthesized by activated T cells and fibroblasts that reflects the patient's inflammatory response status. TNF-α is a class of pro-inflammatory cytokines, mainly formed by macrophages and monocytes, with a significant clinical value for the determination of inflammatory response and stress response in patients. It has been reported that the levels of IL-6 and TNF-α in patients are positively correlated with the inflammatory response in the body. The higher the level, the more pronounced the inflammatory response [7]. In the present study, it was found that IL-6 levels in the acute group significantly increased, indicating that IL-6 could be utilized clinically as a serum marker for interstitial nephritis patients, and it also serves to distinguish the acute phase of interstitial nephritis disease from the chronic phase. Moreover, studies have shown that IL-32 acts on T cells, neutrophils, and other inflammatory cells to release pro-inflammatory factors including interferon and TNF, demonstrating its correlation with the degree of inflammation. Prior research revealed that IL-32, IL-4, and IL-2 induce cytotoxic T cells *in vitro* and enhance their activity and growth cycle. KIM-1 is a transmembrane glycoprotein with very low expression mainly in human kidney tissue. Its level gradually increases 12-24 hours after kidney injury and peaks at 48 hours, so KIM-1 is considered as a critical marker for kidney injury evaluation [24]. This study also demonstrated a positive correlation of serum IL-32 and KIM-1 with SCr and 24 h UPQ. Quinto et al. [3] found that serum IL-32 and KIM-1 were positively cor-

Table 4. Comparison of SCR, ESR, eGFR and 24-h UPQ among 3 groups ($\bar{x}$±sd)

Groups	n	SCr (μmol/L)	ESR (mm/h)	eGFR (mL/min·1.73 m^2)	24 h UPQ (g/L)
Acute Group	42	276.48±20.17	9.84±2.17	41.26±4.36	115.72±6.58
Chronic Group	45	164.62±15.47	5.79±3.62	70.46±6.47	63.41±6.35
Reference Group	40	51.83±17.65	3.24±1.46	96.58±7.58	32.51±5.72
F		31.399	4.162	24.508	23.456
P		<0.01	<0.01	<0.01	<0.01

Note: SCr: serum creatinine; ESR: erythrocyte sedimentation rate; eGFR: estimated glomerular filtration rate; 24 h UPQ: 24-hour urine protein quantity.

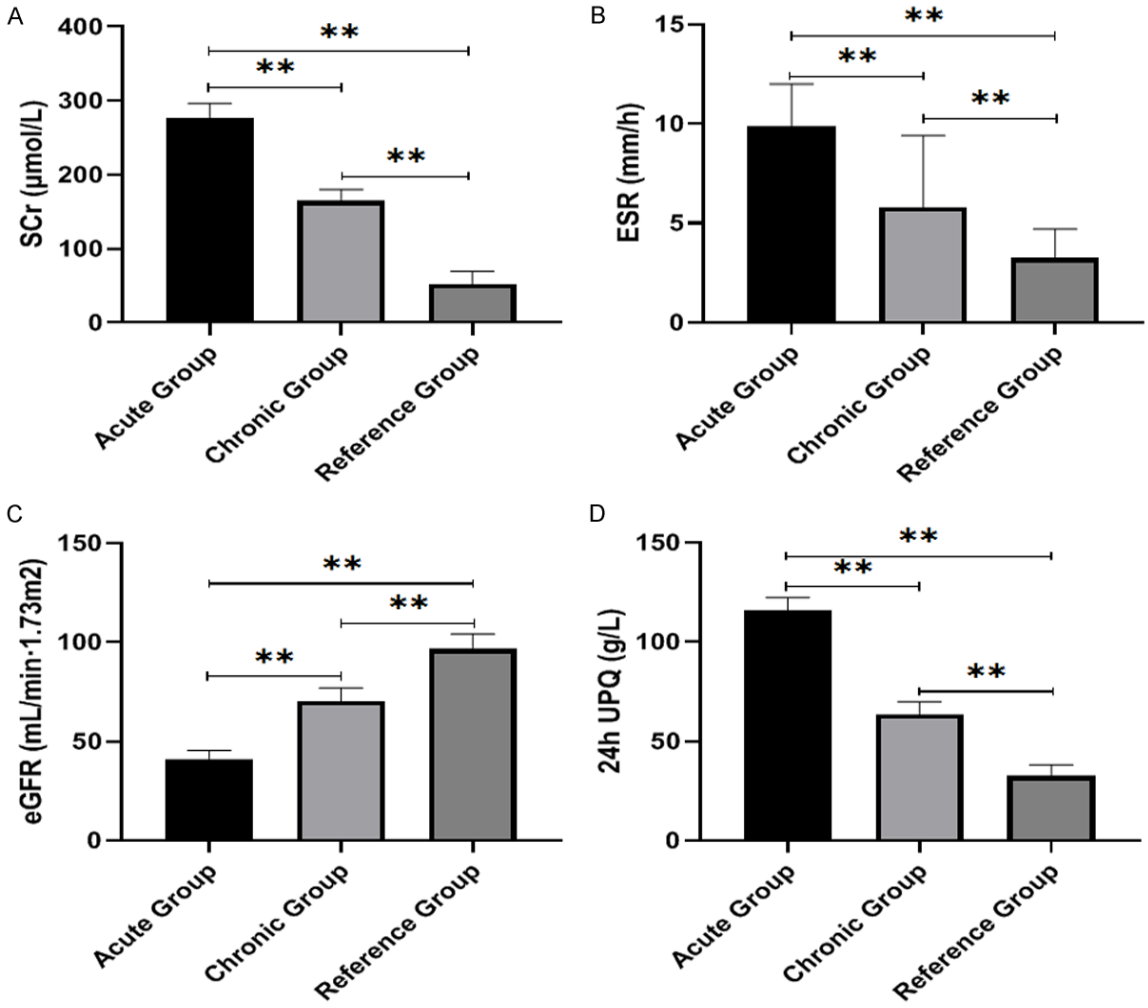

Figure 3. Comparison of SCR, ESR, eGFR and 24-h UPQ among the three groups. Note: A. Changes in serum SCr in the three groups. B. Changes in ESR in the three groups. C. Changes in eGFR in the three groups. D. Changes in 24 UPQ in the three groups. **P<0.01.

related with SCr and 24 h UPQ in patients with active and inactive lupus nephritis, which confirmed that serum levels of IL-32 and KIM-1 can reflect disease severity of interstitial nephritis. The possible mechanism might be that more IL-32 was released into blood with increased inflammatory response, and the active disease process further deteriorated kidney function impairment.

Caravaca-Fontán et al. [5] revealed that acute interstitial nephritis was highly prevalent in elderly patients, while drug-induced acute interstitial nephritis remained the most common

Table 5. Comparison of diagnostic value of single and combined detection of serum IL-6 and TNF-α and mALB

Markers	AUC	P	95% CI	Sensitivity (%)	Specificity (%)
IL-6	0.605	0.092	0.483-0.735	72.43%	52.41%
TNF-α	0.552	0.387	0.427-0.684	57.82%	42.33%
mALB	0.567	0.325	0.441-0.685	64.35%	48.25%
Combination	0.769	<0.001	0.664-0.871	91.72%	54.24%

Note: IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; mALB: micro-albumin.

Table 6. Pearson correlations of IL-32 and KIM-1 with SCr and 24 h UPQ

Index	IL-32		KIM-1	
	r	P	r	P
Acute Group				
SCr	0.635	0.003	0.607	0.002
24 h Urine Protein	0.536	0.014	0.563	0.004
Chronic Group				
SCr	0.604	0.003	0.575	0.004
24 h UPQ	0.559	0.007	0.512	0.009

Note: IL-32: interleukin-32; KIM-1: kidney injury molecule-1; 24 h UPQ: 24-hour urine protein quantity.

Table 7. Comparison of organ function based on TNF-α and IL-6 levels

Levels	TNF-α		t	P	IL-6 (ng/L)		t	P
	≥248.00	<248.00			≥287.20	<287.20		
Cr (μmol/L)	146.72±14.27	95.63±11.58	18.017	<0.001	117.62±17.83	78.72±16.54	10.366	<0.001
BUN (μmol/L)	13.58±3.26	7.46±2.16	10.142	<0.001	11.35±2.65	6.24±1.45	10.963	<0.001
$AaDO_2$ (KPa)	154.37±9.87	103.42±9.67	23.897	<0.001	138.75±4.37	73.42±3.52	75.452	<0.001
PaO_2/FiO_2 (KPa)	30.24±7.82	52.32±8.46	12.421	<0.001	45.34±3.16	56.72±3.42	15.839	<0.001

Note: TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; Cr: creatinine; BUN: blood urea nitrogen; $AaDO_2$: alveolar-arterial oxygen pressure difference; PaO_2/FiO_2: arterial partial pressure of oxygen/fraction of inspired oxygen.

cause. Early discontinuation and corticosteroid therapy remain the mainstay of treatment. Although recent studies have shown that long-term treatment beyond 8 weeks fails to further improve recovery of renal function, and immune allergic reactions to multiple drugs are the most common cause of acute interstitial nephritis, the potential involvement of other underlying systemic diseases should not be neglected. Accordingly, this study was conducted to investigate multiple immune factors and further analyze the mechanism by immune factor expression levels. The limitations of this study lie in the absence of further studies on drug targets as well as long-term follow-up observations, which will be further investigated to provide more reliable results.

Conclusion

In summary, IL-6, with elevated expression in patients with interstitial nephritis, is closely related to disease severity and demonstrates a great potential as an important serum marker for disease progression of interstitial nephritis.

Disclosure of conflict of interest

None.

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