Estimation of sST2 and CXCR3 levels in serum of patients with chronic and acute pyelonephritis caused by *E. coli*

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Abstract:

Background:
Pyelonephritis is a serious and widespread infection of the kidneys, commonly caused by Gram-negative bacteria.This study aims to evaluate the immunomodulatory roles of sST2 and CXCR3 in the blood serum of patients suffering from acute and chronic pyelonephritis.
Objectives:
The main objectives of this study were to:
Investigate the serum levels of sST2 and CXCR3 in patients with acute and chronic pyelonephritis.
Compare the levels of these biomarkers between pyelonephritis patients and healthy controls.
Determine the potential of sST2 and CXCR3 as diagnostic indicators for pyelonephritis.
Materials and Methods:
The study was conducted in Najaf city, Iraq, with a total of 90 participants: 30 patients with acute pyelonephritis, 30 patients with chronic pyelonephritis, and 29 healthy control subjects. Clinical and biochemical tests were performed to confirm the diagnosis of pyelonephritis. Blood serum samples were collected from all participants, and the levels of sST2 and CXCR3 were measured using Enzyme-Linked Immunosorbent Assay (ELISA) technology. Statistical analysis was performed to compare the levels of these biomarkers between the groups.
Results:
The results revealed that both sST2 and CXCR3 levels were significantly elevated ($P < 0.05$) in the serum of patients with pyelonephritis compared to the healthy control group. Additionally, the chronic pyelonephritis group exhibited higher levels of sST2 and CXCR3 ($P < 0.05$) compared to the acute pyelonephritis group, indicating a stronger immune response in chronic cases.
Conclusion:
The study demonstrated that elevated levels of sST2 and CXCR3 are associated with both acute and chronic pyelonephritis. These biomarkers could serve as valuable diagnostic tools for the disease, helping to differentiate between acute and chronic forms of pyelonephritis. The findings suggest that sST2 and CXCR3 play important roles in the immune response to pyelonephritis and may have potential for use in clinical diagnostics.
Keywords: Chemokine Receptor 3 (CXCR3), Tumor suppressor protein 2 (ST2) ,Acute pyelonephritis, Chronic pyelonephritis, *E. coli*

Introduction:

Many studies have revealed the importance of immune markers and some Interleukins in diagnosing many diseases[1], including cancerous tumors]2[**.Tumor suppressor protein 2**

(ST2) is a member of the family of transmembrane interleukin (IL) 1 receptors (ST2L) and soluble isoforms (sST2) that are (over)expressed in several cells under different conditions and following different stimuli (eg. inflammation and stress) [3]. The ligand for ST2 is IL-33, which upon binding to ST2L triggers nuclear signaling and immunological action in various cells (tumor, immune, cardiac), sST2 released into the circulation, acts as a "trap" receptor for IL-33 and inhibits IL-33/ST2L signaling and beneficial effects. The importance and role of the ST2/IL-33 axis and sST2 have been evaluated and confirmed in several inflammatory, cancer, and cardiac diseases [4]. sST2 is involved in the homeostasis/pathogenesis of these diseases, as a counterbalance/response to the activation of the IL-33/ST2L axis, which is turned on and expressed during the development of fibrosis and tissue damage/inflammation and remodeling [5] .Soluble suppressor of tumors 2 (sST2) is the decoy receptor for interleukin (IL)-33. At the time of cellular stress, IL-33 binds to its transmembrane receptor, tumor suppressor 2 (ST2), on Th2 cells, promoting the humoral inflammatory response [5]. In contrast, the soluble isoform of the same receptor regulates IL-33 activity [7].In clinical studies, ST2 (tumor suppressor 2) protein has gained interest as a potential biomarker in cardiovascular disease and is involved in the immune response and is secreted in response to myocardial mechanical overload, thus providing information on remodeling and fibrosis processes, and sST2 has been proposed as a biomarker to predict morbidity and mortality [7]. When evaluated alone, or in combination with other biomarkers (i.e. procalcitonin), including in patients with chronic kidney disease the specific properties of sST2 allow a better assessment of the risk of end-stage renal disease patients undergoing dialysis [9]. sST2, as one of the promising biomarkers of diseases, deserves further study and wider application in clinical practice [10].**Human CXC-Chemokine Receptor 3 (CXCR3)** are a family of molecules consisting of at least 50 different leukocyte chemoattractants, which are produced during lamination and regulate leukocyte migration. Human CXC-Chemokine Receptor 3 (CXCR3) proteins range in length from 68 to 120 amino acids, and have been divided into four structural classes based on the number and arrangement of conserved cysteines: the CXC, CC, and CX3C clusters contain four conserved cysteines, whereas chemokine C (lymphotactin) contains only two [11]. Most CXC chemokines have a chemotactic effect on neutrophils, while CC generally attract monocytes and lymphocytes; Chemokinin C is specific for T and nuture killer (NK) lymphocyte. Human CXC-Chemokine Receptor 3 like CC chemokines, is a potent chemoattractant for monocytes and lymphocytes but not for neutrophils. Leukocytes respond to chemokines through G protein-coupled receptors (GPCRs). These receptors belong to a large and functionally diverse family of proteins that contain seven transmembrane domains (7TMD), common feature of signaling through known chemokine receptors is that their signal transduction pathway leads to the release of Ca21intracellular [12], [13].Human CXC-Chemokine Receptor3 is a chemokine receptor that is highly expressed on effector T cells and plays an important role in T cell trafficking and function [14]. CXCR3 is rapidly induced on naive cells after activation and remains highly preferentially expressed on Th1-type CD4+ T cells and effector CD8+ T cells [15]. In humans, five CXC chemokine receptors (CXCR1–5) have been divided into five separate classes: (1) CXC-restricted, (2) CC-restricted, (3) CC and CXC-restricted, (4) orphan (with non-specific ligands), and (5) viral [16].CXCR3 is activated by three interferon-inducible ligands CXCL9 (MIG), CXCL10 (IP-10), and CXCL11 (I-TAC) [17]. The major chemokine ligands of CXCR3 (CXCL9, CXCL10, CXCL11) have limited expression under homeostatic conditions but are rapidly upregulated by

cytokine stimulation. While CXCL9 is predominantly stimulated by IFN-γ, CXCL10 and CXCL11 can be stimulated by both IFN-γ and type I viruses.

Materials and Methods:

Ethical Consideration

It was approved by the Institutional Ethics Committees of the College of science at the University of Kufa and the Scientific Committee for Research in the Health Department of Najaf. (N.34469-2023).

Patients

The study was conducted in the laboratory of the College of Medical Technologies, Islamic University in Najaf, Iraq, where 89 samples were collected from people distributed into three groups: people with acute pyelonephritis, people with chronic pyelonephritis, and people in normal health in the period between April and December 2023. Ages Participants (18-45 years) All patients were diagnosed by specialist physicians in Al-Hakim General Hospital, as having pyelonephritis, and all samples were collected in sterile conditions. The concentration of the immune marker was measured by an immunoassay called enzyme-linked immunosorbent assay (ELISA) to estimate Human sST2 and Human CXCR3 levels in all groups of subjects.The Human CXCR3 ELISA kit (Catalog No.:EKHU 0070) was and the Human sST2 ELISA kit (Catalog No.: EKHU 0988) by MELSIN / China were used, and were estimated according to the method described by the kit instruction.

The inclusion criteriaand exclusion criteria

The inclusion criteria: pyelonephritis males and females were diagnosed with bacteria *E.coli* in urin culture and no taking drugs.Has been excludedinvolve those who are suffering from acute or chronic diseases,diabetes and subjects taking,smokingand pregnancy

Statistical analysis

SPSS statistical package version 26 was utilized to conduct a data analysis.P-value less than 0.05 considered significantly [18][19]

Results:

In the immunological study, four immunological markers were measured in the serum of three persons (male and female-not pregnant-) groups, age years 18-45 years old as follows; 29 healthy persons as controls, 30 patients with acute pyelonephritis and 30 patients with chronic pyelonephritis caused by the most predominant Multi-drug resistance *E.coli* **(Table 1). Figure (1)** shows the statistical analysis regarding the ages of the healthy control group, which was medium aged (33.31 ± 1.517), and the group with patients infected with pyelonephritis, medium aged (34.35 ± 0.9831), the results showed that there were no statistically significant differences (P 0.6373). While **Figure (2)** indicated that there was no significant increase (P 0.4596) in age in relation to sex (males and females), the medium aged of females was (34.27 ± 1.332), while the medium aged of males was (34.48 ± 1.446). **Figure (3)** Determination of sST2**, t**he results

showed that there was significant increase (P 0.0004) in total sST2 serum concentration in patients infected with pyelonephritis (38.58±4.978 pg/ml) as compared with control (13.06 ± 1.708 pg/ml). **Figure (4)** The Soluble Suppression of Tumorigenicity 2 or (sST2) was measurement in serum of three groups (Figure 4-8), the results showed that there was significant increase (P 0.0142) in sST2 levels in serum of patients infected with acute pyelonephritis (28.59 ± 6588 pg/ml) as compared with control (13.06 ± 1.708 pg/ml) .Also, the results demonstrated that there was a higher sST2 levels in serum of patients infected with chronic pyelonephritis (48.57 ± 7.108 pg/ml) as compared with control with significant differences (P < 0.0001) On the other hand, the results proved that the sST2 levels in serum of patients infected with acute pyelonephritis was highly elevated than sST2 levels in serum of patients infected with chronic pyelonephritis with significant increase (P 0.0218). **Figure (5)** Determination of CXCR 3**,** The results of the present study showed that there was significant increase (P < 0.0001) in total CXCR3 serum concentration in patients infected with pyelonephritis (2887.3±384.8 pg/ml) as compared with control (644.3± 90.16 pg/ml) **Figure (6)** On the other hand, the results demonstrated that there was a significant increase (P 0.0012) in serum concentrations of CXCR3 in patients infected with acute pyelonephritis (2369 ± 528 pg/ml) as compared with control (644.3± 90.16 pg/ml). Also, the results proved that there was higher level of CXCR3in patients infected with chronic pyelonephritis (3406 ± 552.4 pg/ml) as compared with control with significant differences (P < 0.0001) While, the results of the current study indicated that there was no significant differences (P 0.0900) of CXCR3 levels in serum of patients infected with acute pyelonephritis and chronic pyelonephritis. **Table (2)** shows a positive correlation between CXCR3 and sST2.with a significant difference p = 0.023.

Table (1) Numbers and percentages of health individuals and patients in this study

Persons	Sex	Age (year)				
		(18-25)	(26-35)	(36-45)	Total (100%)	
Acute pyelonephritis caused by *E.coli*	Female	6	7	8	21(70)	30(34)
	Male	2	2	5	9(30)	
Chronic pyelonephritis caused by *E.coli*	Female	3	5	6	14(46.6)	30(34)
	Male	1	6	9	16(53.4)	
Healthy Controls	Female	1	8	4	13(45)	29(32)
	Male	6	3	7	16(55)	
Total (100%)		19(21)	31(35)	39(44)	89(100)	

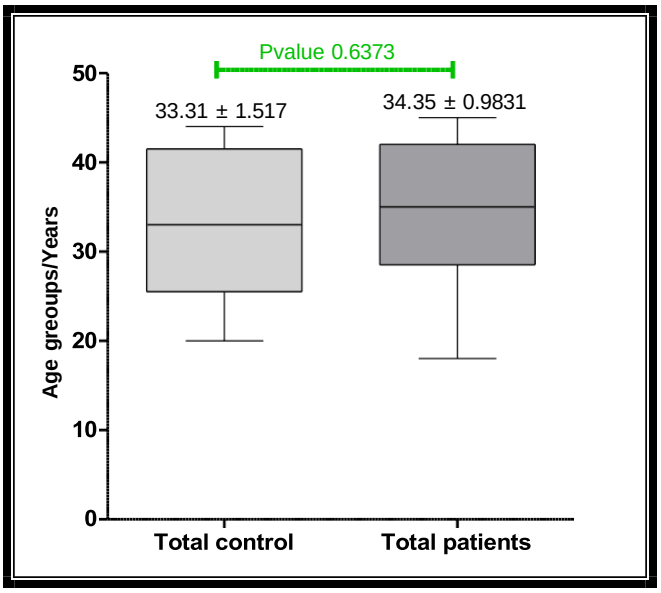

Figure (1) Medium of age in pyelonephritis patients and healthy controls

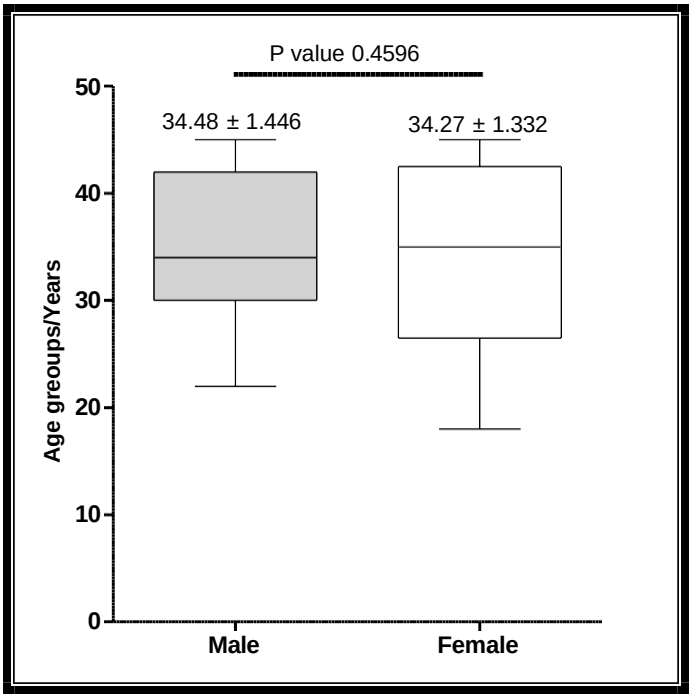

Figure (2) Medium of age in total female and male

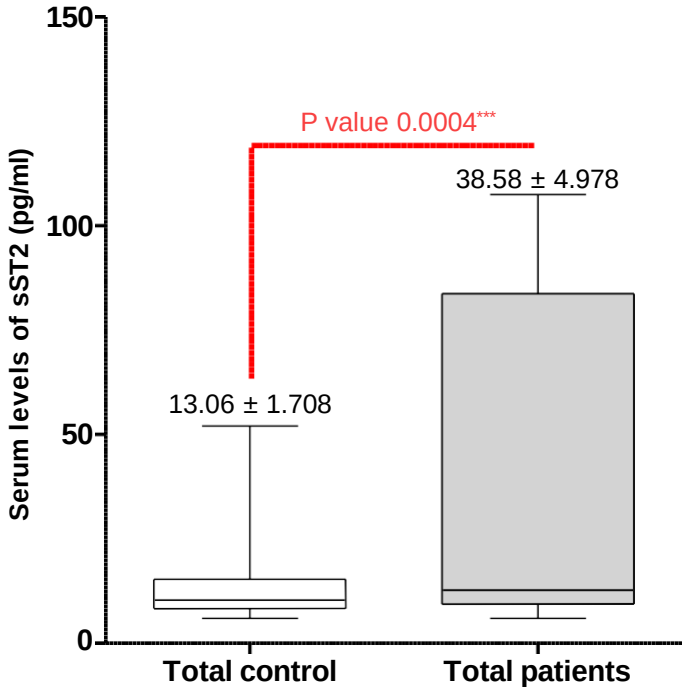

Figure (3) sST2 levels in serum of total patients infected with pyelonephritis control.

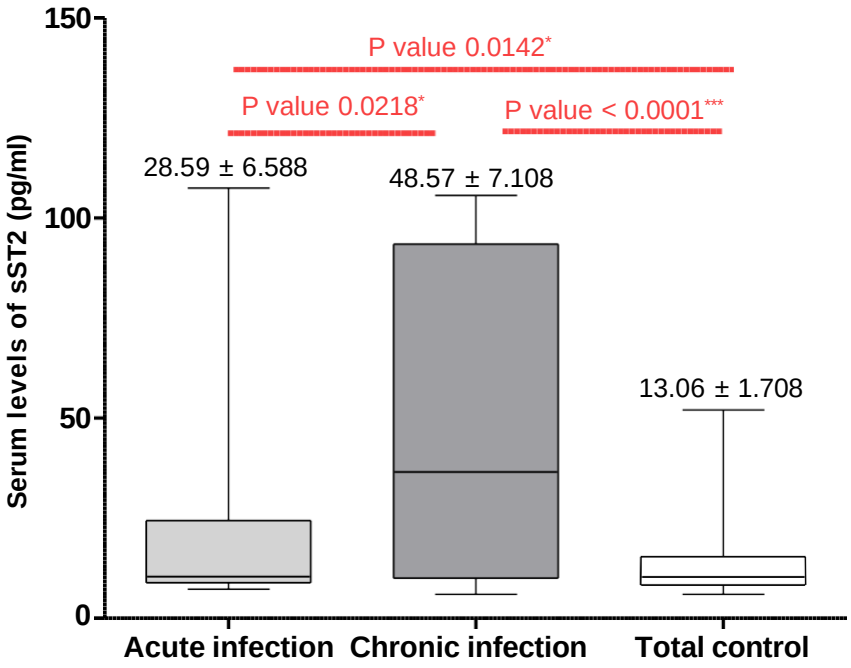

Figure (4) sST2 levels in serum of patients infected with acute and chronic pyelonephritis and control.

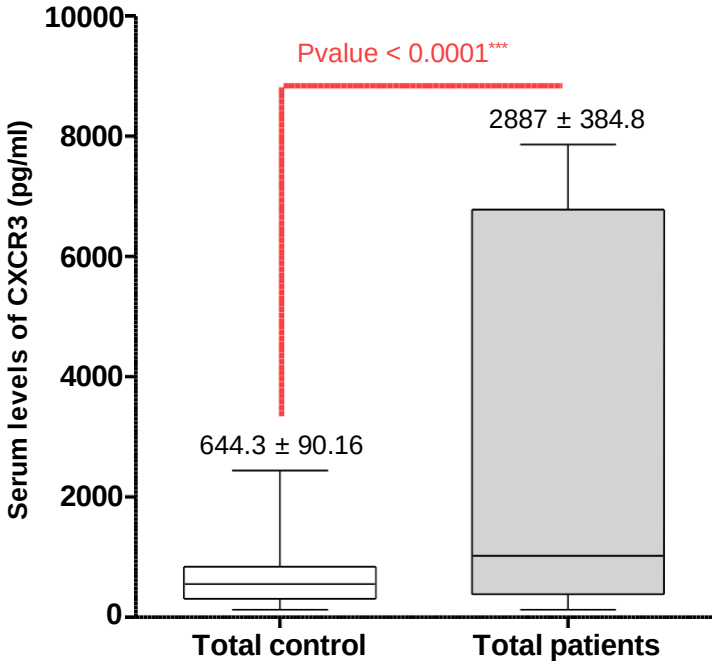

Figure (5) CXCR3 levels in serum of total patients infected with pyelonephritis and control.

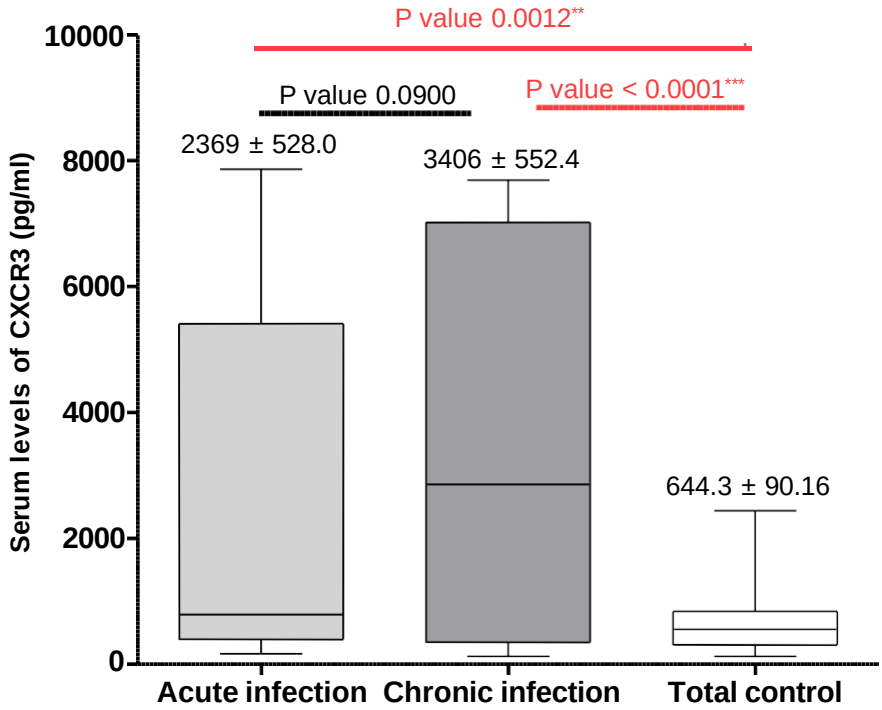

Figure (6) CXCR3 levels in serum of patients infected with acute and chronic pyelonephritis and control.

Table (2) Descriptive Statistics and correlation between CXCR3 and sST2.

Biomarkers	Mean	Std. Deviation	Correlations	Sig. (1-tailed)	Number
CXCR3	3405.9810	3025.5607	0.368**	0.023	30
sST2	48.5733	38.93364			30

(* Correlation is significant at the 0.05)

Discussion:

Pyelonephritis infections has been studied as one of the most common kidney diseases, especially in Iraq, specifically in Najaf Governorate, and it affects females, males, and all ages. [20]. In our study, the age of the patient was defined in a specific category from 18 to 45, because at these ages their immune system was complete, in addition to that they did not suffer from other functional diseases when compared to elderly people over 50 years of age[21]. The MCP-3 immune marker was studied for what It has an important action and effect against infections in general [22]. This is what became clear to us when its percentage in patients was much higher and with a significant difference when compared to healthy people. It also increased proportionally with the progression of the disease, so the results showed that patients with chronic kidney inflammation were more Concentration in patients with acute kidney disease, which indicates its action is similar to some interlequins, which are increased in chronic diseases when compared with acute diseases [23]. The immune response against pyelonephritis plays a crucial role in protecting the host from pathogenic invasion, as it helps to prevent recurrent infections and maintain overall urinary tract healt.Thus, understanding the intricacies of this immune response can inform targeted treatment strategies and improve patient outcomes. One key aspect of this immune response involves the activation of various immune cells, such as neutrophils and macrophages, which work together to eliminate the invading pathogens and facilitate tissue repair at the site of infection [24]. Clinical symptoms of pyelonephritis depend on the local and systemic host response to the presence of microbes such as Gram-negative and Gram-positive bacteria in the upper urinary tract [25]. In addition, the release of high concentrations of pro-inflammatory cytokines in serum and/or urine leads to a systemic response and the appearance of some symptoms such as fever and increased signs of inflammation or a local response such as proteinuria, pyuria and erythrocytosis [26]. Virulence, resistance, and dispersal factors as well as recontamination with epizootic bacteria may come into play some diseases develop, whether acute or chronic [27]. Although innate immune responses play essential roles in the first line of host defense against pathogens, they also cause harm when they are present in excess or dysregulated [28]. For example, in acute conditions, urothelial cells and inflammatory cells, in response to UPEC stimulation, produce several pro-inflammatory mediators cause epithelial inflammation/damage. , allowing bacteria to enter underlying tissues [29]. In addition, if

neutrophil activation is not strictly regulated, reactive, cytotoxic enzymes and ingested bacteria can be released into the surrounding area of inflammation, causing cell and tissue destruction and the dissemination of pathogens [35]. CXCR3 is a chemokine receptor that is highly expressed on effector T cells and plays an important role in T cell trafficking and function. CXCR3 is rapidly induced on naïve cells following activation and preferentially remains highly expressed on Th1-type CD4+ T cells and effector CD8+ T cells. CXCR3 is activated by three interferon-inducible ligands CXCL9 (MIG), CXCL10 (IP-10) and CXCL11 (I-TAC) [32]. The results of the present study showed that patients of pyelonephritis infections had much higher serum sST2 concentrations than controls with significant increase ($P < 0.0001$). Suppression of Tumorigenicity 2 (sST2) is a member of the IL-1 receptor family and it consists of two important isoforms namely, ST2 ligand (ST2L) and soluble ST2 (sST2) [33], ST2L is a transmembrane receptor while sST2 is a soluble receptor that circulates in the bloodstream. sST2 has been to an important role in the pathogenesis of different cardiovascular diseases [34]. Higher concentrations of sST2 were associated with disease progression and predicted prognosi [35] .The development of biomarkers that can identify kidney disease early is a translational research priority as failure of therapeutic trials in kidney disease is widely believed to be due the dependence on serum creatinine, a late marker of kidney injury to diagnose kidney disease. Multiple studies have suggested sST2 to be one of the most powerful prognostic biomarkers in both acute and chronic heart failure [10].At the time of cellular stress, IL-33 binds to its transmembrane receptor, suppressor of tumorigenicity 2 (ST2) on Th2 cells, promoting a humoral inflammatory response, by contrast, the soluble isoform of the same receptor modulates IL-33 activity [36].Additionally, the production of cytokines and chemokines aids in recruiting more immune cells to the site of infection, further enhancing pathogen clearance and inflammation resolution [37].The results of the present study showed that patients of pyelonephritis infections had much higher serum CXCR3 concentrations than controls with significant increase ($P < 0.0001$). Most CXC chemokines are chemotactic for neutrophils, CXCR3 is a chemokine receptor that is highly expressed on effector T cells and plays an important role in T cell trafficking and function [38]. CXCR3 is rapidly induced on naïve cells following activation and preferentially remains highly expressed on Th1-type CD4+ T cells and effector CD8+ T cells. CXCR3 is activated by three interferon-inducible ligands CXCL9 (MIG), CXCL10 (IP-10) and CXCL11 (I-TAC) [32].Given the association between the CXCR3 system and inflammation, it is perhaps not surprising that CXCR3 and its ligands also play a role in a variety of autoimmune diseases [39]. Play the CXCR3-starting and intensifying the inflammatory events, and it is released in the beginning of inflammatory

Conclusions

In Iraq - Najaf Governorate - the results of the current study indicated that there are significant differences in the levels of sST2 and CXCR3 in serum patients with pyelonephritis when compared with healthy controls, also showed that sST2 and CXCR3 is related correlation positive to pyelonephritis and can be used to help in diagnose the disease.

References:

[1] W. R. O. Alfatlawi, M. K. Khudhair, and J. A. Ali, "Detection and role of some interleukins and tumor necrotic factor alpha among patients with tuberculosis," *Med. J. Babylon*, vol. 21, no. 4, pp. 878–883, 2024.

[2] K. W. A. Khattab, N. S. Alazzo, and B. B. Mohammed, "The Evaluation of CD10 and HER2 Immunohistochemical Markers in Urothelial Carcinoma of Urinary Bladder," *Med. J. Babylon*, vol. 21, no. 4, pp. 869–877, 2024.

[3] J. Chen, P. Xiao, D. Song, D. Song, Z. Chen, and H. Li, "Growth stimulation expressed gene 2 (ST2): Clinical research and application in the cardiovascular related diseases," *Front. Cardiovasc. Med.*, vol. 9, p. 1007450, 2022.

[4] E. Homsak and D. Gruson, "Soluble ST2: A complex and diverse role in several diseases," *Clin. Chim. acta*, vol. 507, pp. 75–87, 2020.

[5] M. H. Ali, S. Z. Nada, and L. A. Darwish, "The role of sST2 as biochemical markers for cardiac fibrosis in patients with Myocardial Infarction," *NeuroQuantology*, vol. 20, no. 9, p. 5746, 2022.

[6] L. Shakerian *et al.*, "IL-33/ST2 axis in autoimmune disease," *Cytokine*, vol. 158, p. 156015, 2022.

[7] R. Ghali, "The role of interleukin-33 (IL-33) administration in cardiac function post-myocardial infarction." Université Paris Cité, 2020.

[8] M. Dudek *et al.*, "sST2 and Heart Failure—Clinical Utility and Prognosis," *J. Clin. Med.*, vol. 12, no. 9, p. 3136, 2023.

[9] N. Bansal *et al.*, "Cardiac biomarkers and risk of incident heart failure in chronic kidney disease: the CRIC (Chronic Renal Insufficiency Cohort) Study," *J. Am. Heart Assoc.*, vol. 8, no. 21, p. e012336, 2019.

[10] J. Li *et al.*, "A review of novel cardiac biomarkers in acute or chronic cardiovascular diseases: the role of soluble ST2 (sST2), lipoprotein-associated phospholipase A2 (Lp-PLA2), myeloperoxidase (MPO), and procalcitonin (PCT)," *Dis. Markers*, vol. 2021, 2021.

[11] C. Perpiñá Viciano, "Study of the activation mechanisms of the CXC chemokine receptor 4 (CXCR4) and the atypical chemokine receptor 3 (ACKR3)." Universität Würzburg, 2020.

[12] C. Mazzotti *et al.*, "The atypical receptor CCRL2 (CC Chemokine Receptor-Like 2) does not act as a decoy receptor in endothelial cells," *Front. Immunol.*, vol. 8, p. 296752, 2017.

[13] D. Capoferri, "In vitro pharmacological characterisation of the role of ACKR3 on CXCR4-dependent and-independent function." University of Glasgow, 2020.

[14] X. Wang *et al.*, "The role of CXCR3 and its ligands in cancer," *Front. Oncol.*, vol. 12, p. 1022688, 2022.

[15] M. A. M. Ayala *et al.*, "CXCR3 expression in regulatory T cells drives interactions with type I dendritic cells in tumors to restrict CD8+ T cell antitumor immunity," *Immunity*, vol. 56, no. 7, pp. 1613–1630, 2023.

[16] M. Miao, E. De Clercq, and G. Li, "Clinical significance of chemokine receptor antagonists," *Expert Opin. Drug Metab. Toxicol.*, vol. 16, no. 1, pp. 11–30, 2020.

[17] J. Korbecki *et al.*, "The role of CXCR1, CXCR2, CXCR3, CXCR5, and CXCR6 ligands in molecular cancer processes and clinical aspects of acute myeloid leukemia (AML)," *Cancers (Basel).*, vol. 15, no. 18, p. 4555, 2023.

[18] D. R. A. Al-Janabi, A. A. Fattah, A. A. J. Aljanaby, and W. H. Alhissnawy, "Comparison of Some Blood Parameters and Vitamin D3 for Patients with Pyelonephritis and Renal Failure in Najaf Governorate, Iraq," *Ren. Fail.*, vol. 91, no. 50.93, p. 10.

[19] D. R. A. Al-janabi, Y. A. Shallani, L. A. D. Albakaa, and A. A. J. Aljanaby, "Prevalence of types of cancer in Najaf Governorate and comparison of leukemia with other types," *J.*

Biomed. Biosens., vol. 4, no. 2, pp. 1–10, 2024.
[20] D. R. A. Al-janabi and A. A. J. Aljanaby, "Comparison of Escherichia coli and Proteus mirabilis in patients infected with chronic pyelonephritis in Al-Najaf Governorate, Iraq," in *BIO Web of Conferences*, EDP Sciences, 2024, p. 6006.
[21] H. M. H. Al-aaraji, M. R. Mansor, and D. R. A. Al-janabi, "The role of IL-6, IL-8 and TNF-α in COVID-19 patients in Karbala Governorate," in *E3S Web of Conferences*, EDP Sciences, 2023.
[22] S. Singh, D. Anshita, and V. Ravichandiran, "MCP-1: Function, regulation, and involvement in disease," *Int. Immunopharmacol.*, vol. 101, p. 107598, 2021.
[23] S. M. Y. Mhana and A. A. J. Aljanaby, "Bacteriological and Immunological study of kidney failure patients infected with urinary tract infections," in *E3S Web of Conferences*, EDP Sciences, 2023, p. 3110.
[24] P. F. Surai and A. Surai, "Silymarin and immunity," in *Silymarin Puzzle*, Wageningen Academic, 2023, pp. 249–285.
[25] L. Schwartz, J. de Dios Ruiz-Rosado, E. Stonebrook, B. Becknell, and J. D. Spencer, "Uropathogen and host responses in pyelonephritis," *Nat. Rev. Nephrol.*, vol. 19, no. 10, pp. 658–671, 2023.
[26] P. Gauckler, J. Il Shin, G. Mayer, and A. Kronbichler, "Eosinophilia and kidney disease: more than just an incidental finding?," *J. Clin. Med.*, vol. 7, no. 12, p. 529, 2018.
[27] F. Admasu and M. Wakjira, "Pathology of Epizootic-Infectious Diseases of Fishes in Aquaculture," *Biomed. J. Sci. Tech. Res.*, vol. 40, no. 2, pp. 31984–31995, 2021.
[28] Q. Zhang and X. Cao, "Epigenetic regulation of the innate immune response to infection," *Nat. Rev. Immunol.*, vol. 19, no. 7, pp. 417–432, 2019.
[29] K.-Y. Wu *et al.*, "The C5a/C5aR1 Axis contributes to the pathogenesis of acute cystitis through enhancement of adhesion and colonization of uropathogenic E. coli," *Front. Cell. Infect. Microbiol.*, vol. 12, p. 824505, 2022.
[30] I. Miralda and S. M. Uriarte, "Periodontal Pathogens' strategies disarm neutrophils to promote dysregulated inflammation," *Mol. Oral Microbiol.*, vol. 36, no. 2, pp. 103–120, 2021.
[31] A. D. Kennedy and F. R. DeLeo, "Neutrophil apoptosis and the resolution of infection," *Immunol. Res.*, vol. 43, pp. 25–61, 2009.
[32] J. R. Groom and A. D. Luster, "CXCR3 in T cell function," *Exp. Cell Res.*, vol. 317, no. 5, pp. 620–631, 2011.
[33] C.-P. Chang, M.-H. Hu, Y.-P. Hsiao, and Y.-C. Wang, "ST2 signaling in the tumor microenvironment," *Tumor Microenviron. Role Interleukins–Part A*, pp. 83–93, 2020.
[34] C. Ip *et al.*, "Soluble suppression of tumorigenicity 2 (sST2) for predicting disease severity or mortality outcomes in cardiovascular diseases: A systematic review and meta-analysis," *IJC Hear. Vasc.*, vol. 37, p. 100887, 2021.
[35] M. Li *et al.*, "Prognostic value of soluble suppression of tumorigenesis-2 (sST2) for cardiovascular events in coronary artery disease patients with and without diabetes mellitus," *Cardiovasc. Diabetol.*, vol. 20, pp. 1–11, 2021.
[36] M.-R. Choi, J. A. Sosman, and B. Zhang, "The janus face of IL-33 signaling in tumor development and immune escape," *Cancers (Basel).*, vol. 13, no. 13, p. 3281, 2021.
[37] Y. Cho and G. Szabo, "Two faces of neutrophils in liver disease development and progression," *Hepatology*, vol. 74, no. 1, pp. 503–512, 2021.
[38] N. Karin, "CXCR3 ligands in cancer and autoimmunity, chemoattraction of effector T cells, and beyond," *Front. Immunol.*, vol. 11, p. 541785, 2020.
[39] K. Van Raemdonck, P. E. Van den Steen, S. Liekens, J. Van Damme, and S. Struyf, "CXCR3 ligands in disease and therapy," *Cytokine Growth Factor Rev.*, vol. 26, no. 3, pp. 311–327, 2015.