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Exploring Immunological Markers In Urinary Tract Infection: An Investigation The Level Of IL6, IL17 And TNF Alpha

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Abstract

Background: Urinary tract infections (UTIs) are frequently caused by bacterial infections, which vary in frequency depending on age and gender. Five percent of all fever cases are caused by it. Infection may be limited to the inferior portion of the urinary tract (UT) or may include the kidney's parenchyma as the first location of bacterial infection.
Aims: This study aimed to evaluate the relationship between the levels of Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-17 (IL-8) in UTI cases across various bacterial species.
Methodology: A total of 160 urine and blood samples were obtained from UTI patients aged 20 to over 60, along with 65 urine and blood samples from healthy individuals as a control group. After promptly inoculating each urine sample on a blood agar plate and a MacConkey agar plate with a sterile loop, the samples were incubated aerobically for 24 hours at 37°C. To measure the levels of human cytokines (IL-6, IL-17, and TNF-α) in the patient and control groups, an Enzyme-Linked Immunosorbent Assay (ELISA) kit was utilized.
Results: Positive bacterial growth was isolated from urine samples, and the results indicated extremely significant differences between the species specified ($P < 0.001$). Of all the positive isolates, E. coli had the highest percentage at 25 (38.46), whereas proteus species had 16 (24.61%). Analysis of serum levels of IL6, IL17, and TNF-a in UTI patients compared to control showed a significantly significant increase in IL6 levels in UTI patients compared to healthy controls ($p < 0.001$).
Conclusion: According to the findings of this study, elevated levels of TNF-a, IL6, and IL17 in UTI patients over the course of infection may be helpful as diagnostic biomarkers.

Key words: urinary tract infection, interleukin6, Tumor necrosis factor.

1. Introduction

Urinary tract infections (UTIs) are among the most common bacterial illnesses(Taha, 2024). Every year, more than $6 billion USD is spent on UTI diagnoses, which impact 150 million individuals globally (Zeng et al., 2022). The spectrum of UTI diseases ranges from simple cystitis to serious infections including pyelonephritis and associated side effects (Kaur & Kaur, 2021). UTIs are frequently more common in women than in males because the female urethra is physically less efficient at preventing bacterial invasion (Magliano et al., 2012). Furthermore, a lot of factors influence the frequency rate of UTIs, such as age, previous antibiotic therapy, hospitalization, and catheterization. Over 95% of urinary tract infections are caused by a single type of bacteria, as is widely recognized. E. coli is the bacteria that most commonly causes acute illnesses (Tandogdu, Z., & Wagenlehner, 2016). According to some research conducted in Iraq, the most common pathogenic organisms that cause UTIs were Klebsiella pneumonia, E. coli, and Staphylococcus species, all of which were resistant to the most widely used

medications (Naqid et al., 2020). The incidence of morbidity is decreased by early UTI treatment with first-line antibiotics. To provide a successful empirical therapy, it is crucial to comprehend the main microorganisms causing UTIs and their corresponding patterns of antibiotic resistance (Alfetlawi & Jasim, 2022). Approximately fifty per cent of people get recurrent UTIs, which are characterized as occurring several times in a year or twice in six months (Kranz et al., 2024; Calin et al.,2024). The prevalence of UTI is equal for both sexes in the neurogenic bladder environment, however some patient populations are more susceptible than others, such as those with neurological bladders or bladders that are dysfunctional owing to central or peripheral neurological impairment (Dinh et al., 2016).

The coordination of inflammatory reactions depends on tiny proteins called cytokines (Minasyan, 2019). One of the most significant and effective cytokines in pro-inflammatory responses is TNF-α. It has previously been documented that TNF-α has a role in the pathophysiology of allograft rejection, glomerulonephritis, shistosoma haematobium-induced urinary tract morbidity, pediatric febrile infections, and the monitoring of the therapeutic response to BCG in bladder cancer (Mohkam et al., 2013). Numerous cells, such as macrophages, fibroblasts, endothelial cells, and renal tubular epithelial cells, produce the pro-inflammatory cytokine interleukin-6 (IL-6). As a pyrogen that manifests early in the inflammatory process, it causes the acute-phase response, which includes fever and the heightened synthesis of acute phase proteins such C-reactive protein. During inflammation, it is also a major inducer of B and T-cell activation and development (Krzemień et al., 2016). Six molecules with similar structures (IL-17A to IL-17F) make up the cytokine family IL-17, with IL-17A and IL-17F having the closest functional relationships. A dimeric receptor made up of pairs of five subunits IL-17RA through IL-17RE is how IL-17 cytokines are signaled (Amatya et al., 2017). Both homodimeric and heterodimeric forms of IL-17 and IL-17F can communicate via the obligatory dimeric IL-17RA and IL-17RC receptor complex (Bagri et al., 2022).

There is an obvious unmet need for trustworthy immunological biomarkers that might improve early diagnosis, direct clinical decision-making, and potentially provide mechanistic insights, given the diagnostic limits of current markers, which include delayed culture findings and vague symptoms. A targeted investigation into these three cytokines may provide useful biomarkers for the identification of infections and further our knowledge of the inflammatory pathways involved in the pathophysiology of UTIs.

2. Material & Methods

2.1. Sample collection:

Each of the participants had a 20mL calibrated sterile screw-capped universal cup filled with clean catch midstream urine, which was then given to the patients. Within six hours, the samples were tagged, brought to the lab, and examined. To stop germs from growing in urine samples, 0.2 mg of boric acid was applied to each container. In order to prevent urethral contamination, all patients received thorough instruction on how to collect samples aseptically beforehand. After receiving the necessary ethical permission and being reviewed by the hospital administration, the study was carried out.

2.2. Isolation of clinical samples:

This study involved urine samples from 160 patients, 72 of whom were male and 88 of whom were female, who visited the inpatient and outpatient departments (OPDs) of Al Najaf Teaching Hospital, Al Zahraa Teaching Hospital, and Al Sader Medical City in the Al-Najaf Governorate over a ten-month period (March–June 2025) and who, according to urologists, had clinical signs of a urinary tract infection. Patients in the research were between the ages of 20 and 60. The research did not include individuals receiving antibiotic medication. In order to examine the immunological markers and compare them with those of the healthy group, five milliliters of blood were also drawn from suspicious people.

2.3. Sample processing:

To isolate bacterial pathogens from urine samples, a calibrated loop approach was employed. A calibrated sterile platinum wired loop measuring 4.0 mm was utilized to distribute 0.001 mL of urine. As a conventional procedure for isolation and purification, a loopful of urine was plated on nutritional agar after being inoculated on blood agar, MacConkey agar, and Cystine-Lactose-Electrolyte Deficient (CLED) agar (Mahon & Lehman, 2022). For 24 hours and 48 hours, respectively, in the negative instances, the infected plates were incubated at 37°C. To estimate the bacterial load/mL of the urine

sample, the number of isolated bacterial colonies was multiplied by 1000. Pure isolates were obtained by subculturing each urine sample that showed a considerable growth of bacteria, and the isolates were then identified using biochemical assays.

2.4. Automated Identification by using the Vitek®2 system:

Bacterial species were accurately identified using the Vitek®2 system (bioMérieux, France). 64 biochemical assays are included in the method to diagnose microorganisms (Maugeri et al., 2019).

2.5. Immunological markers:

Using ELISA, serum obtained from 2 milliliters of venous blood drawn from individuals suspected of having a UTI was analyzed. Out of 160 samples, only 65 individuals with a positive UTI infection had their serum interleukin levels measured and compared to a healthy matched group. The ELISA kit instructions (Elabscience, USA) were strictly followed in order to assess the levels of IL-6, IL-17, and TNF-a.

2.6. Statistical Analysis:

The Statistical Package for Social Science (SPSS) version 22 for Windows was used to conduct the statistical analysis, and Graphpad Prism9 was used to create the graphics. Frequencies were used to summarize qualitative data including age, sex, education level, and place of residence. The independent t-test was used to summarize continuous data, including IL6, IL17, and TNF-a levels, by mean and standard deviation. The chi-square test was performed to identify differences between qualitative and analytical data. A p-value of less than 0.05 was deemed statistically significant.

3. Results & Discussion

Results:

A microbiological study was performed on 160 cases that were clinically classified as urinary tract infections. Of these, 65 instances (40.62%) had considerable uropathogen growth, whereas the remaining cases (59.38%) had either negligible bacteriuria or no growth. According to Table (1), the age distribution of the high percentage positive increase was in the group >60 (25%) and the group 51-60 (21.87%), with substantial distinctions (P <0.001). According to the report, women made up 88 percent of the population. The study's majority of patients had elementary education levels of 78 (48.75%) and secondary education levels of 54 (33.75%). Among those who lived in rural areas, 102 (63.75%) were compared to 58 (36.25%) in cities, with significant differences (p <0.001).

Table (1): general characteristics of study population.

Variables	Study samples (160)			Statistical evaluation	
	Groups	No.	%	χ^2	p. value
Age (years)	20-30	25	15.63	340.1	**<0.001*** **
	31-40	28	17.5		
	41-50	32	20		
	51-60	35	21.87		
	>60	40	25		
Sex	Male	72	45	134.0	**<0.001**
	Female	88	55		
Education	Primary	78	48.75	250.3	**<0.001**
	Secondary	54	33.75		
	University	28	17.5		
Residence	Rural	102	63.75	154.2	**<0.001**
	City	58	36.25		

χ^2 **:** chi-square test**; *****:** highly significant.

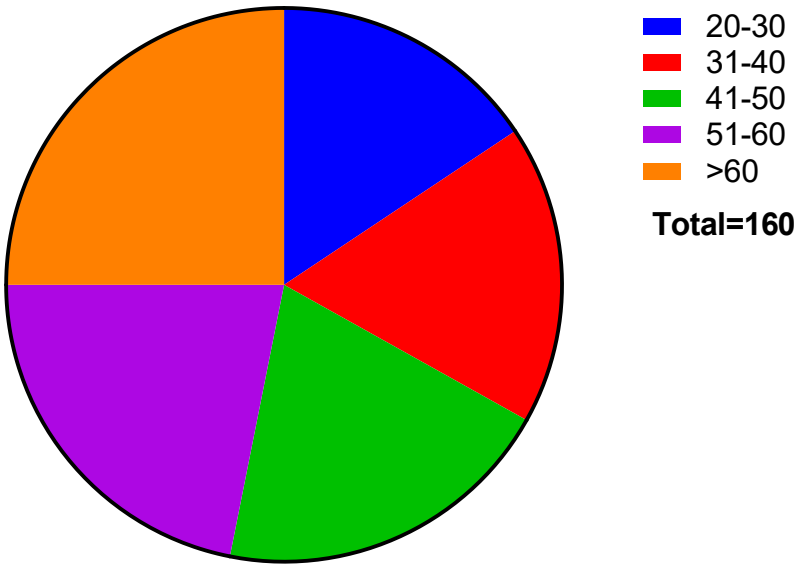

Figure (1): age groups distribution of study population.

As seen in figure (2), among patients with positive bacterial growth, females (64.6%) were nearly twice as impacted as men (35.4%). This variation is considered significant (P <0.05; Chi-square= 4.089).

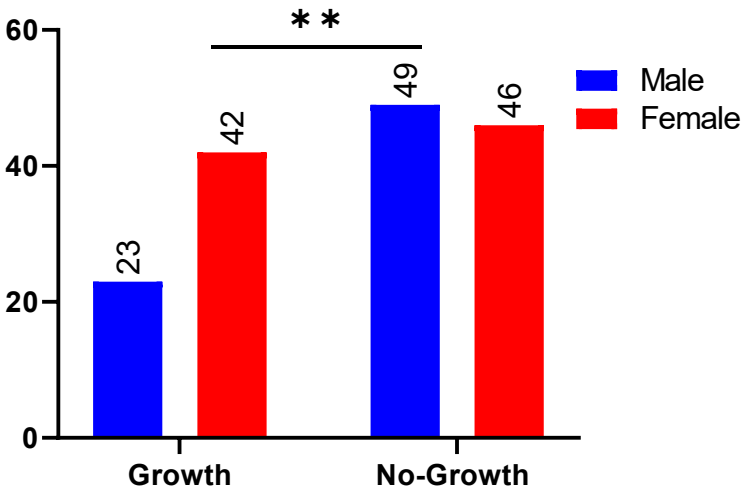

Figure (2): bacterial growth distribution across sex of studied population.

In the growing group, elementary school students made up the largest percentage (53.8%), followed by secondary school students (32.3%), and university students (13.9%). According to figure (3), the difference in educational attainment was not statistically noteworthy (Chi: 1.486; p. value: ns).

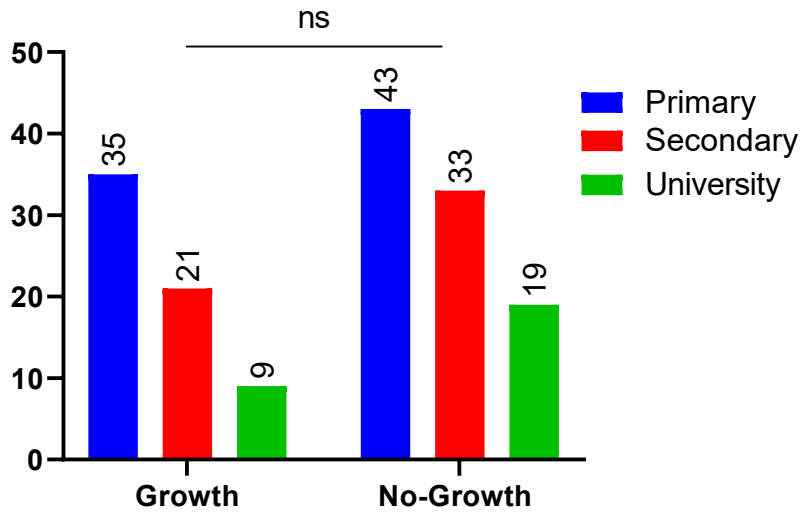

Figure (3): bacterial growth distribution across educational levels of studied population.

According to Figure (4), the growth group's instances were statistically significant (Chi-square 3.469; p. value: <0.05), with the majority (72.3%) occurring in rural regions and the fewest (20.7%) occurring in cities.

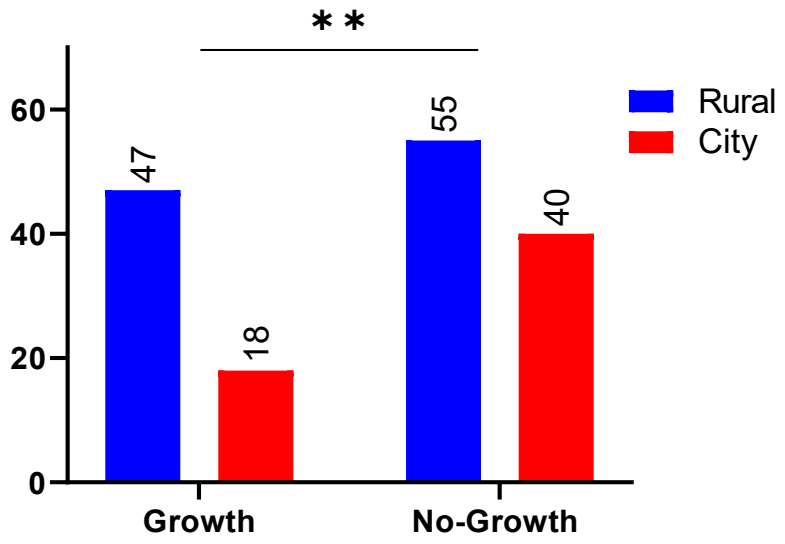

Figure (4): bacterial growth distribution across residency of studied population.

As Table (2) illustrates, the group aged 60 and above has the largest percentage of positive growth (35.39%), while the group aged 20 to 30 has the lowest (9.24%). Despite the apparent steady rise in positive culture rates with age, this trend is not statistically significant ($p > 0.05$).

Table (2): growth distribution across age groups.

Age groups	Total samples (N.160)		Positive growth (N. 65)		Statistical evaluation	
	N	%	N	%	χ^2	p. value
20-30	25	15.63	6	9.24	3.613	0.461ns

31-40	28	17.5	9	13.84		
41-50	32	20	12	18.46		
51-60	35	21.87	15	23.07		
>60	40	25	23	35.39		
Total	160 (100%)		65 (100%)			
χ^2 **:** chi-square test**; ns:** non-significant.						

There were extremely significant differences between the species described in Table (3), which displayed positive bacterial growth isolated from urine samples (P <0.001). Proteus species accounted for 16 (24.61%) of all positive isolates, but E. coli ranked first with a high proportion of 25 (38.46), as seen in figure (5).

Table (3): isolated bacterial species from clinical samples.

Isolated bacterial species	**Total positive samples (N. 65)**		**Statistical evaluation**	
	N	**%**	χ^2	**p. value**
E.coli	25	38.46	140.02	**<0.001*** **
Proteus spp.	16	24.61		
Klebsiella pneumonia	10	15.38		
Staphylococcus spp.	8	12.30		
Serratia marcescens	6	9.23		
χ^2 **:** chi-square test**; *****:** highly significant.				

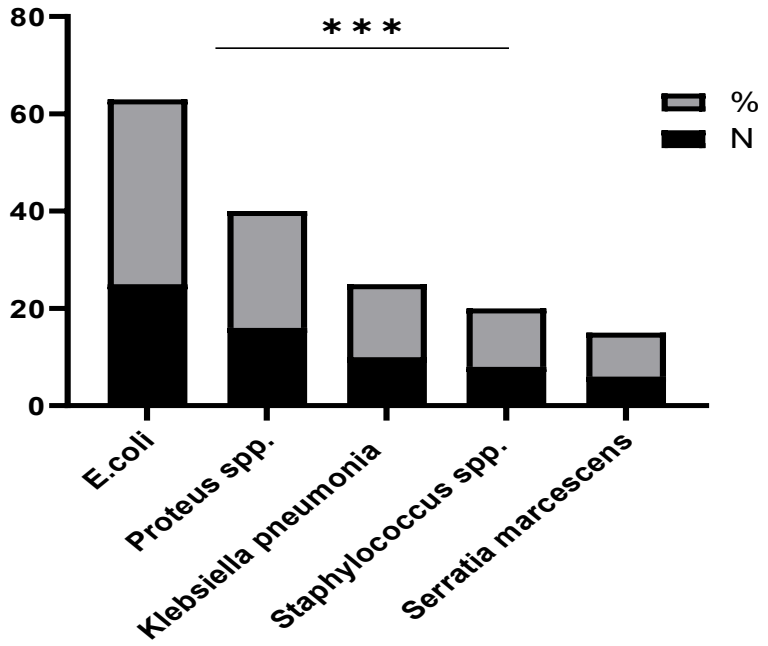

Figure (5): isolated bacterial species from urine samples.

As illustrated in figure (6), table (4) showed the findings of blood level IL6 concentration among UTI patients in comparison with control and showed a highly significant rise in IL6 levels across UTI patients when in comparison with healthy control ($p < 0.001$).

Table (4): serum level of IL6 among patients with UTI and healthy control.

Study group	Comparison of serum IL6 pg/ml			P. value
	Mean ± SD	t. test	95% C.I	
Patients (N. 65)	78.65 ± 12.08	6.12	8.09- 25.32	**<0.001*** **
Control (N. 65)	23.04 ± 5.22			
SD: standard deviation**; IL6:** interleukin-6**; C.I:** confidence interval**; ***:**highly significant differences.				

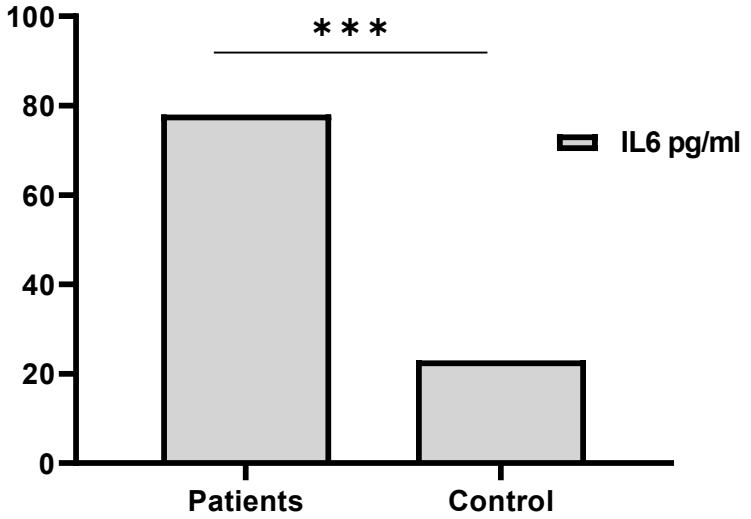

Figure (6): serum IL6 level among UTI patients and control.

Serum levels of TNF-a and IL17 in UTI patients were compared to control in Tables (5) and (6). Additionally, an extremely significant rise in IL6 levels was found in UTI patients in contrast to healthy controls ($p < 0.001$), as illustrated in Figures (7) and (8), consequently.

Table (5): serum level of IL17 among patients with UTI and healthy control

Study group	Comparison of serum IL17 pg/ml			P. value
	Mean ± SD	t. test	95% C.I	
Patients (N.65)	149.05 ± 34.6	8.38	26.22- 38.23	**<0.001*** **
Control (N.65)	65.13 ± 12.4			
SD: standard deviation**; IL17:** interleukin-17**; C.I:** confidence interval**; ***:**highly significant differences.				

Table (6): serum level of TNF-a among patients with UTI and healthy control.

Study group	Comparison of serum TNF-a ng/ml			P. value
	Mean ± SD	t. test	95% C.I	
Patients (N.65)	195.22 ± 66.7	12.82	13.04- 22.34	**<0.001*** **
Control (N.65)	72.33 ± 24.03			
SD: standard deviation**; TNF-a:** tumor necrosis factor-alpha**; C.I:** confidence interval**; ***:**highly significant differences.				

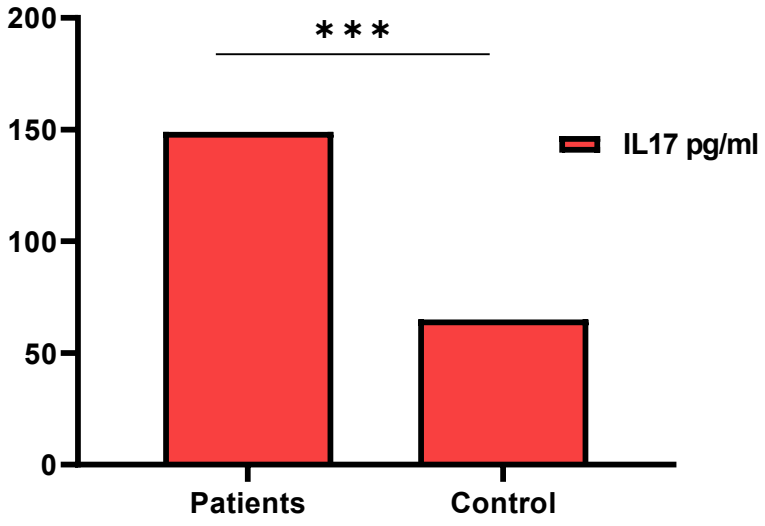

Figure (7): serum IL17 level among UTI patients and control.

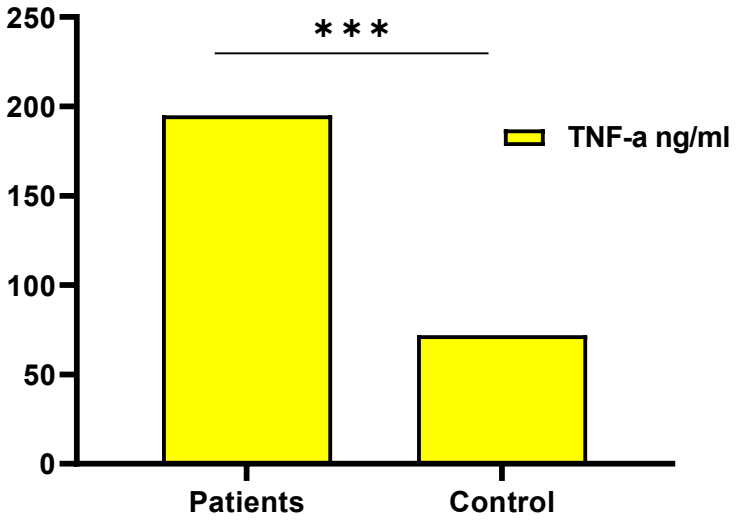

Figure (8): serum TNF-a level among UTI patients and control.

4. Discussion

The most frequent cause of hospitalization for bacterial infections and the most prevalent illness among the elderly worldwide are urinary tract infections (UTIs) (Nasrollahian et al., 2024). According to the present study, elderly individuals are more likely than younger people to get urinary tract infections (UTIs) because of high rates of urinary retention, urinary incontinence, prolonged hospital stays, comorbidities, concurrent urinary catheterizations, and deteriorating immune responses (Li et al., 2017). Diabetes mellitus, urinary catheterization, urinary tract abnormalities, especially in those with urinary retention or incontinence (e.g., prostatic hyperplasia), and sexual activity the main risk factor for both men and women in older age are configurable causes for UTIs in older adults (Akhtar et al., 2021). The analysis of the data in the current investigation showed that, in comparison to men, women continue to account for the majority of UTI cases, which is mostly corroborated by earlier research (Naqid et al., 2020; Ibrahim et al.,2021). The results confirm that women are still more susceptible to UTIs because of their fundamental anatomy, which places their urethra closer to the anal orifice and shorter than men's (Tan & Chlebicki, 2016). Once more, women's susceptibility may be exacerbated by hormonal changes throughout the menstrual cycle and a potential hereditary component that tends to run in families (Omwenga et al., 2021). Most research revealed that gram-negative bacteria, not gram-positive ones, were more frequently responsible for UTI cases (Sierra-Díaz et al., 2019), which are in line with the present study. The high frequency of UTIs may be due to the existence of particular virulence factors in gram-negative bacteria, such as adhesion proteins and distinctive structures that make it easier for the bacteria to connect to uroepithelial cells (Govindarajan & Kandaswamy, 2022). Moreover, Johnson et al., (2021) found that urinary tract infections were more common in people with lower educational attainment. UTIs are linked to malnutrition, inadequate personal cleanliness, and low socioeconomic level, all of which are prevalent in the countryside (Bitew et al., 2017). Although a wide variety of germs can cause UTIs, Escherichia coli and other Enterobacteriaceae are the most prevalent pathogens in the population that cause uncomplicated UTIs, accounting for around 75% of isolates (Ibrahim et al., 2020).

Current research analysis showed that UTI patients had higher levels of IL6 than controls, which is consistent with D'asheesh et al., (2020). The production of interleukin-6 (IL-6) occurs in response to tissue injury or infection. It is a cytokine that promotes inflammation and activates the innate and adaptive immune systems. As part of the innate immune response, leukocytes and stromal cells release IL-6 when pattern recognition receptors are triggered. After then, IL-6 draws immune cells and starts the B and T cell response (Al Kabe et al., 2018). According to Nanda & Juthani-Mehta, (2009), in order to determine serum IL-6's potential as a biomarker for urinary tract infection detection, a large population study is required. As a possible biomarker for UTI detection, Mohammed & Alrifai, (2021) examined the level of IL6 in UTI patients and discovered that it dramatically rose during infection.

Numerous antibacterial pathways are started by IL-17, such as the production of chemokines and antimicrobial peptides, the activation and recruitment of neutrophils and monocytes, and the possible direct destruction of infected cells (Papotto et al., 2017). Significantly, most of the few studies that document IL-17 expression in UTIs involve bacteria other than UPEC, such Proteus, Streptococcus, Schistosoma, or Candida (Scharff et al., 2019). It has been demonstrated that IL-17 plays no part in the bladder's adaptive immune response. On the other hand, γδ+ T cells' production of IL-17 promotes the early removal of germs from the diseased bladder. The capacity of IL-17 to produce the cytokines and chemokines required to promote the infiltration of neutrophils and other innate effectors in the bladder was thought to be the cause of its protective action. Deficient cytokine and chemokine transcripts, as well as compromised neutrophil and macrophage influx during infection, are probably the causes of this clearance deficiency. Mice lacking γδ+T cells had heightened vulnerability to UTI, which is consistent with our finding (Ibrahim & Al-Hashimy, 2022). TNF-α is a key modulator of the acute inflammatory response against pathogenic microorganisms, including Gram-negative bacteria, and is accountable for the systemic problems that result from severe infections. LPS triggers Gram-negative bacteria's cell walls to produce TNF-α for production. In severe infections, TNF is generated in high quantities, which results in systemic problems (Mohkam, 2020). The current study's findings demonstrated that the group of individuals with UTIs caused by bacterial infections had higher blood levels of TNF-α. This suggests that the bacterially caused inflammation in UTIs activates TLR4 macrophages and triggers the generation of TNF-α. The generated TNF-α contributes to the activation of leukocyte integrins and endothelial cell integrin ligands, increasing the leukocytes' adhesion to the endothelium and subsequent migration into extravascular tissues where they fight off microorganisms (Susilaningsih et al., 2012).

5. Conclusion

According to our research, target cytokines are important in UTI, particularly during the acute phase. Significant differences in UTI infection were also seen in age group, sex, and place of residence. Additionally, there is significant data that suggests elevated levels of IL-6, IL-17, and TNFα in UTI patients, which may be used as diagnostic biomarkers.

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