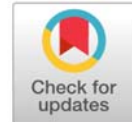


Comparative Evaluation of Complications in Untreated and Recurrent Urinary Tract Infections

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ABSTRACT

Background: Urinary tract infections (UTIs) are common but can cause severe complications if untreated or recurrent, affecting renal function and antibiotic resistance. This study uniquely uses biomarkers such as CRP, NGAL, IL-6, and TNF- α to predict renal dysfunction and antibiotic resistance, highlighting their clinical significance.

Objectives: To compare the complications of untreated and recurrent UTIs concerning renal function, systemic inflammation, oxidative stress, and antibiotic resistance using biomarker analysis.

Methods: A comparative study was conducted on 500 adult patients (2022–2023) from two tertiary care hospitals. Patients were categorized into recurrent UTIs (≥ 3 episodes/year) and untreated UTIs (≥ 1 month without antibiotics). Biomarkers for renal dysfunction (creatinine, eGFR, NGAL), inflammation (CRP, IL-6, TNF- α , procalcitonin), and oxidative stress (MDA, KIM-1) were analyzed. Multivariate regression and statistical tests assessed predictors and significance.

Results: Untreated UTIs were associated with significantly worse renal outcomes (creatinine: 2.1 ± 0.4 mg/dL, eGFR: 54.2 ± 6.1 ; $p < 0.001$), higher inflammation (CRP: 35.7 ± 5.9 mg/L; procalcitonin: 2.1 ± 0.6 ng/mL; $p < 0.001$), and elevated oxidative stress (MDA: 6.7 ± 1.3 $\mu\text{mol/L}$). Recurrent UTIs had higher multidrug resistance rates (45% vs 28%, $p = 0.002$). CRP, NGAL, and procalcitonin independently predicted renal dysfunction, while IL-6 and TNF- α were strong predictors of antibiotic resistance.

Conclusions: Untreated UTIs pose severe risks for renal health and systemic inflammation, while recurrent UTIs increase antibiotic resistance. Biomarkers offer valuable predictive tools for early intervention, improving patient outcomes.

Keywords: Urinary tract infections, biomarkers, renal function, inflammation, oxidative stress, antibiotic resistance.



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INTRODUCTION

Millions of people around the globe suffer from urinary tract infections (UTIs) every year. While many UTIs can be effectively treated, recurrent and untreated infections are clinically significant and pose serious risks, particularly for renal function and systemic health. Repeated or inadequately treated UTIs are strongly associated with chronic kidney disease (CKD), urosepsis, and the emergence of antibiotic-resistant pathogens [1]. Untreated or recurrent UTI is a major burden for both patients and health care systems. Untreated infections can

progress to upper urinary tract infection (pyelonephritis) and irreversible renal damage, especially in patients with recurrent infections [2]. Also, repeated courses of antibiotics for UTI increase the emergence of multidrug resistant organisms, making management difficult and increasing the cost of healthcare. The global overuse and misuse of antibiotics has accelerated resistance and exacerbates this problem[3].

The most dangerous form of untreated UTIs is urosepsis, when the infection spreads from the urinary tract into the blood stream. In addition, it is very dangerous,

especially for the immunocompromised patients and patients with pre-existing comorbidities. Recurrent and untreated UTIs have a major impact on patients' quality of life, and can lead to organ failure and death, unless urosepsis is treated [4]. Persistent symptoms, frequent visits to the doctor, and chronic pain, as well as long term anxiety about permanent damage to the kidneys all contribute to psychological distress. Many patients that have real fear of future infections and what shall happen in consequence, suffer from strong emotional stress and even decreased overall well being [5]. Antibiotic resistance has become a global health crisis. Antibiotic resistance is one of the world's greatest public health threats, according to the World Health Organization. UTIs are but one critical example where effective treatment can be delayed in resource limited settings. The spread of resistant bacterial strains that cause recurrent infections has been worsened even further by the inappropriate use of antibiotics to manage UTIs. UTI has been the focus of a great deal of research, but there are no biomarkers that predict complications like renal dysfunction, systemic inflammation or resistance to antibiotics [6]. Specifically, CRP, NGAL, IL-6 and TNF- α biomarkers have tremendous potential as early detection and management biomarkers for these complications. In order to address this critical gap, this study utilizes a comprehensive biomarker assay for disease progression and improved patient outcomes. This study aims to determine the complications of recurrent and untreated UTIs and assess specifically how these are affected on renal function, systemic inflammation, antibiotic resistance and quality of life. This study attempts to improve the early detection and management of UTI related complications and prevention by analysing a diverse panel of biomarkers, providing actionable insights for clinicians and public health strategies [7].

MATERIALS AND METHODS

A comparative study was conducted to evaluate the complications of recurrent and untreated urinary tract infection (UTI) in adult patients. A total of $n = 500$ participants ≥ 18 years old were recruited from the Urology and Nephrology wards of the two tertiary care hospitals of Central Park Teaching Hospital, Lahore and Arif Memorial Teaching Hospital Kasur, Pakistan from October, 2022 – September, 2023. The Institutional Review Boards of participating hospital approved the study (IRB Approval: Ethical clearance was obtained (RLKUMC/IRB/0050/2024). All participants gave written informed consent and patient data was anonymized. Strict inclusion and exclusion criteria were used in the selection of participants. Eligibility was for adults with a documented clinical history of recurrent UTIs, recurrent UTIs, defined as three or more episodes in a 12-month period, or persistent untreated UTIs, persisting for one month or longer without antibiotic intervention. To limit

confounding variables, we excluded pregnant patients, immunosuppressed patients, those undergoing cancer treatment and those with other forms of systemic infections other than UTIs. A power analysis indicated that a minimum of $n = 250$ subjects in each group would be sufficient to achieve 80% statistical power ($p = 0.05$) to detect clinically significant differences between the recurrent UTI and untreated UTI groups with an effect size of 0.5. A total of 500 participants were enrolled accounting for potential dropouts and missing data. Selection bias was minimized by performing consecutive sampling, and standardized protocols were used for data collection and laboratory analysis.

Demographic data, medical history and information regarding the duration and frequency of UTI episodes were collected from all participants. Renal function was calculated as serum creatinine, blood urea nitrogen (BUN) and calculated estimated glomerular filtration rate (eGFR) by the CKD-EPI formula. Clinical symptoms, including fever and hypotension, and laboratory findings, including positive blood cultures, elevated procalcitonin and increased CRP were used to diagnose urosepsis.

A comprehensive panel of 25 biomarkers was analyzed to assess the severity of infection and the contributions of systemic inflammation, renal damage and oxidative stress. To ensure accuracy and reliability of data, blood samples were collected and processed, analyzed using enzyme linked immunosorbent assays (ELISA), high performance liquid chromatography (HPLC) and standard biochemistry analysers in accredited laboratories. However, serum creatinine, BUN, eGFR, CRP, procalcitonin, neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule. Urine samples were analyzed for causative pathogens, and antimicrobial susceptibility testing was performed by standard Clinical and Laboratory Standards Institute guidelines. Multidrug resistant organisms (MDROs) were defined as those isolates resistant to at least three classes of antibiotics. Different stages of the study were used to employ bias minimization strategies. Selection bias was reduced through consecutive sampling and laboratory protocols followed standardized methods to minimize measurement error. For continuous variables missing data was addressed with mean imputation, and outliers were identified via boxplots and winsorized to preserve data integrity. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY). Continuous variables were presented as means with standard deviations, while categorical variables were expressed as frequencies and percentages. Independent t-tests compared continuous variables between the recurrent and untreated UTI groups, while Chi-square tests analyzed categorical variables. Multivariate linear regression models were constructed to evaluate associations between biomarker levels and clinical outcomes, including renal function decline,

systemic inflammation, and multidrug-resistant organisms. The interaction effects of UTI type and biomarker levels on renal outcomes, urosepsis risk, and antibiotic resistance patterns were assessed using two-way analysis of variance (ANOVA), with Tukey's post-hoc test applied to identify significant group differences. A p-value of ≤ 0.05 was considered statistically significant in all analyses. Laboratory quality assurance protocols were strictly followed, and all data were anonymized to protect patient confidentiality. Ethical considerations were maintained throughout the study, adhering to institutional guidelines and international ethical standards.

RESULTS

In the study, a total of n=500 participants were enrolled, n=250 in the recurrent UTI group and n=250 in the untreated UTI group. The mean age of the patients was 47.6 (± 14.3) years and 67% were female. Age (46.9 \pm 13.8 years vs. 48.3 \pm 14.5 years, $p = 0.481$) or gender distribution (68% female vs. 66% female recurrent vs. untreated, $p = 0.674$) were not statistically different between the recurrent and untreated UTI groups as shown in table-1 and Fig-1.

Renal Function: There were huge differences in renal function between the two groups. Serum creatinine levels were higher in the untreated UTI group (2.1 \pm 0.4 mg/dL) than in the recurrent UTI group (1.6 \pm 0.3 mg/dL; $p < 0.001$), indicating worse renal function in untreated patients. To the contrary, the eGFR was significantly lower in the untreated group (54.2 mL/min/1.73m² \pm 6.1) compared with the recurrent UTI group (72.5 mL/min/1.73m² \pm 7.4) ($p < 0.001$). Levels of blood urea nitrogen (BUN) were also significantly higher in the untreated group (30.5 mg/dL \pm 5.9) than in the recurrent group (22.3 mg/dL \pm 4.7; $p < 0.001$). The results show that untreated UTIs were associated with significantly worse renal function.

Inflammatory Markers: Systemic inflammation was greater as indicated by elevated inflammatory biomarkers (C-reactive protein CRP and procalcitonin) in the untreated UTI group. Untreated patients had higher CRP levels (35.7 mg/L \pm 5.9) than patients with recurrent UTI (22.4 mg/L \pm 4.8) ($p < 0.001$). In addition, procalcitonin levels were

significantly higher in the untreated UTI group (2.1 ng/mL \pm 0.6) than in the recurrent UTI group (1.4 ng/mL \pm 0.3) ($p < 0.001$). Interleukin-6 (IL-6) levels were also elevated in the untreated group (41.9 pg/mL \pm 6.2) compared to the recurrent group (28.7 pg/mL \pm 5.4) ($p < 0.001$), reflecting higher levels of systemic inflammation in untreated cases.

Oxidative Stress and Tissue Damage: Markers of oxidative stress, such as malondialdehyde (MDA), and kidney injury molecule-1 (KIM-1), were significantly higher in the untreated UTI group, suggesting greater oxidative damage and renal tissue injury. MDA levels were elevated in the untreated group (6.7 μ mol/L \pm 1.3) compared to the recurrent group (4.2 μ mol/L \pm 0.9) ($p < 0.001$). Similarly, KIM-1 levels were higher in untreated UTI patients (3.7 ng/mL \pm 0.9) than in recurrent UTI patients (2.5 ng/mL \pm 0.6) ($p < 0.001$).

Antibiotic Resistance: More frequently isolated in the recurrent UTI group were multidrug resistant organisms (MDROs). Of 45% of patients in the recurrent group, compared with 28% of patients in the untreated group ($p = 0.002$), 45% had MDRO infections. Inflammatory markers, including IL-6 and tumor necrosis factor alpha (TNF- α), were strongly associated with the presence of MDROs, as shown by regression analysis. Patients with MDROs had higher IL-6 levels (38.5 pg/mL \pm 6.1) than patients without MDROs (27.9 pg/mL \pm 5.8) ($p < 0.001$) and similarly elevated TNF- α levels (32.7 pg/mL \pm 5.4) as compared to patients without MDROs (23.1 pg/mL \pm 4.5) ($p < 0.001$).

Multivariate Regression Analysis: The effects of biomarkers on key outcomes, such as renal dysfunction (measured by serum creatinine), inflammation (measured by CRP), and the presence of MDRO were assessed using multivariate linear regression. It found that CRP, procalcitonin and neutrophil gelatinase associated lipocalin (NGAL) were significant independent predictors of renal dysfunction. The R² adjusted for renal dysfunction was 0.42, meaning that these biomarkers accounted for 42% of the variance in renal function outcomes. Like IL-6 and TNF- α , MDRO presence was an independent significant predictor, with an adjusted R² of 0.35 as shown in table-2.

Table 1: Baseline Characteristics and Key Biomarkers in Recurrent and Untreated UTI Groups

Parameter	Recurrent UTI Group (Mean \pm SD)	Untreated UTI Group (Mean \pm SD)	p-value
Age (years)	46.9 \pm 13.8	48.3 \pm 14.5	0.481
Gender (Female %)	68%	66%	0.674
Serum Creatinine (mg/dL)	1.6 \pm 0.3	2.1 \pm 0.4	< 0.001
eGFR (mL/min/1.73m ²)	72.5 \pm 7.4	54.2 \pm 6.1	< 0.001
Blood Urea Nitrogen (BUN, mg/dL)	22.3 \pm 4.7	30.5 \pm 5.9	< 0.001
C-reactive Protein (CRP, mg/L)	22.4 \pm 4.8	35.7 \pm 5.9	< 0.001
Procalcitonin (ng/mL)	1.4 \pm 0.3	2.1 \pm 0.6	< 0.001
Neutrophil Gelatinase-Associated Lipocalin (NGAL, ng/mL)	160.3 \pm 28.4	215.7 \pm 32.1	< 0.001
Kidney Injury Molecule-1 (KIM-1, ng/mL)	2.5 \pm 0.6	3.7 \pm 0.9	< 0.001
Malondialdehyde (MDA, μ mol/L)	4.2 \pm 0.9	6.7 \pm 1.3	< 0.001
Interleukin-6 (IL-6, pg/mL)	28.7 \pm 5.4	41.9 \pm 6.2	< 0.001

Tumor Necrosis Factor-α (TNF-α, pg/mL)	23.4 ± 4.1	35.1 ± 5.0	< 0.001
Uric Acid (mg/dL)	5.7 ± 0.9	8.1 ± 1.4	< 0.001
Serum Ferritin (ng/mL)	175.8 ± 32.1	231.7 ± 39.2	< 0.001

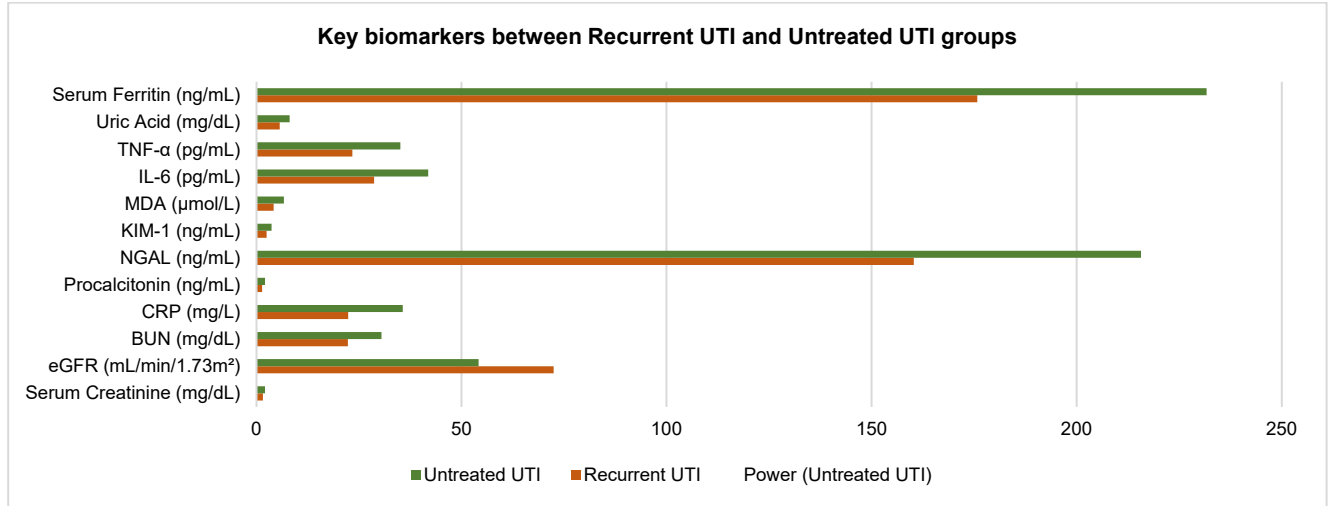
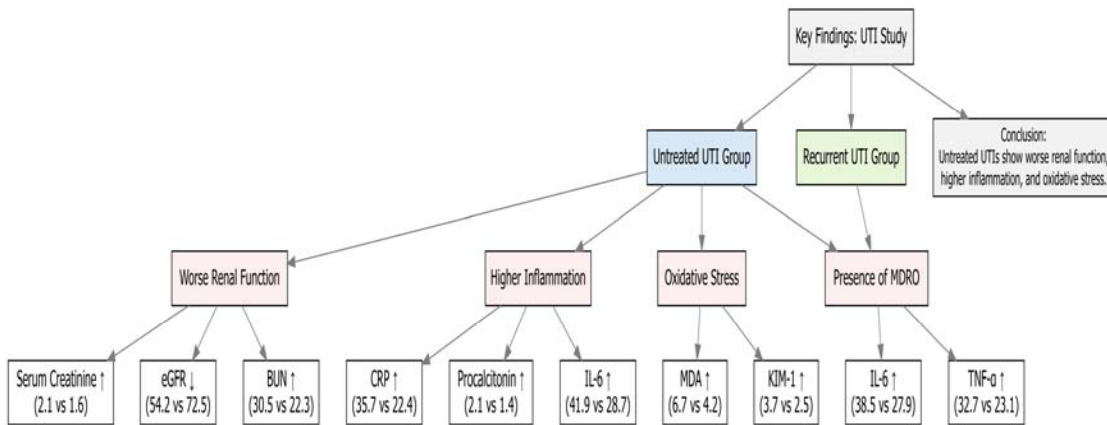


Figure 1: Comparative analysis of key biomarkers between Recurrent UTI and Untreated UTI group: The graph illustrates significantly worse renal function (Serum Creatinine, eGFR, BUN), higher inflammation (CRP, Procalcitonin, IL-6, TNF-α), and increased oxidative stress (MDA, KIM-1) in the Untreated UTI group compared to the Recurrent UTI group, emphasizing the need for timely intervention.

Table 2: Multivariate Linear Regression Analysis Predicting Renal Dysfunction, Inflammation, and Presence of MDROs

Dependent Variable	Independent Variable (Biomarkers)	β Coefficient	Standard Error	p-value	Adjusted R ²
Renal Dysfunction (Creatinine)	C-reactive Protein (CRP, mg/L)	0.231	0.034	< 0.001	0.42
	Neutrophil Gelatinase-Associated Lipocalin (NGAL, ng/mL)	0.451	0.028	< 0.001	
	Procalcitonin (ng/mL)	0.212	0.029	< 0.001	
	Blood Urea Nitrogen (BUN, mg/dL)	0.356	0.031	< 0.001	
Inflammation (CRP, mg/L)	Interleukin-6 (IL-6, pg/mL)	0.389	0.041	< 0.001	0.38
	Tumor Necrosis Factor-α (TNF-α, pg/mL)	0.329	0.039	< 0.001	
Presence of MDROs	Interleukin-6 (IL-6, pg/mL)	0.287	0.045	< 0.001	0.35
	Tumor Necrosis Factor-α (TNF-α, pg/mL)	0.311	0.047	< 0.001	
	Uric Acid (mg/dL)	0.198	0.031	0.002	



This study found that untreated UTIs are significantly more associated with worse renal function, higher inflammatory biomarkers levels and greater oxidative stress compared to recurrent UTIs. The presence of multidrug resistant organisms, independent predictors of

IL-6 and TNF alpha, and elevated levels of CRP, procalcitonin, and NGAL remained independent predictors of renal dysfunction. These findings emphasize the importance of early intervention to prevent long term complications and antibiotic resistance associated with

UTIs. The fig-2 represents key findings of the UTI study are summarized in this flowchart: In the Untreated UTI group, there was elevation of serum creatinine, BUN, eGFR, systemic inflammation (CRP, procalcitonin, IL6) and oxidative stress (MDA, KIM1). In addition, the recurrent UTI group was showed to have had higher levels of IL-6 and TNF α , and was more likely to contain multidrug resistant organisms (MDROs).

DISCUSSION

The results of this study provide critical understanding of the complications of untreated and recurrent urinary tract infections (UTIs) including renal function, systemic inflammation, oxidative stress, and multidrug resistant organism (MDRO) prevalence. Unlike recurrent UTI, clinical course of UTIs without treatment was more severe, characterized by significantly worse renal outcomes, increased inflammatory markers and higher oxidative stress. That's in keeping with previous research that shows that can result in permanent kidney damage and systemic infection [8].

Serum creatinine, blood urea nitrogen(BUN) and reduced estimated glomerular filtration rate (eGFR) are the common parameters of renal impairment due to untreated UTI [9]. The most likely reason for the accelerated decline is that prolonged infection and sustained inflammation are associated with declining renal function. Biomarkers such as kidney injury molecule (KIM) 1 and neutrophil gelatinase associated lipocalin (NGAL) indicate structural injury to the renal system and reflect early-stage renal injury. These markers are elevated and represent significant tubular damage reflecting progression of untreated UTIs to chronic kidney disease (CKD) [10].

Untreated UTIs were associated with more pronounced inflammatory responses characterized by significantly increased CRP, procalcitonin and IL-6. These biomarkers are strong systemic immune activation indicators, with elevated CRP and procalcitonin indicating the increased risk of urosepsis [11]. Untreated infections urgently need timely identification and management of inflammation to prevent severe systemic complications. In addition, untreated UTIs cause sustained inflammation, which causes further renal damage and contributes to a milieu that promotes the growth of multidrug resistant organisms [12]. Another important finding in untreated UTIs was

oxidative stress, as indicated by elevated malondialdehyde (MDA). Increased MDA levels represent lipid peroxidation, a process that results in damage of tissue and cells in chronic infections. Oxidative stress further combined with inflammation accelerates renal dysfunction and underscores the importance of targeting both mechanisms in therapeutic interventions. Further evidence of severe tubular epithelial injury in untreated infections is confirmed by elevated KIM-1 levels [13].

Multidrug resistant organisms like *Escherichia coli* and *Klebsiella pneumoniae* were strongly associated with recurrent UTIs although less severe in the renal impairment. Patients with recurrent infections probably develop resistance through repeated exposure to antibiotics. High recurrent UTIs levels of tumor necrosis factor-alpha (TNF- α) and IL-6 indicate that inflammatory conditions contribute in choosing resistant bacterial strains. This highlights the need for antibiotic stewardship program implementation and alternative treatment options to mitigate the emergence of resistance [14, 15]. Our findings suggest that biomarkers including CRP, NGAL, procalcitonin, IL-6, and TNF- α can be used to assist in clinical decision making. These biomarkers represent valuable tools for the identification of patients at risk of severe renal impairment and antibiotic resistance, enabling clinicians to intervene earlier and optimize treatment strategies. Biomarker analysis can be incorporated into routine clinical practice and may improve outcomes of patients with recurrent and untreated UTI by allowing focused management and monitoring [16].

This study has limitations but despite its strengths. Without a prospective design, causal relationships between biomarker levels and clinical outcomes cannot be established. Furthermore, limitations of generalizing the findings to other, broader, or less specialized healthcare settings are also present due to recruitment of the study population from two tertiary care hospitals. These findings need to be validated with further research, including longitudinal studies in diverse populations, and their long term implications need to be assessed in biomarker guided management of UTIs [17].

This study contributes to a growing body of evidence highlighting the role of biomarkers in understanding the progression and complications of UTIs. Addressing inflammation, oxidative stress, and antibiotic resistance through early intervention and targeted therapies is essential to improving clinical outcomes and reducing the healthcare burden associated with these infections [18].

CONCLUSION

This study emphasizes the negative consequences of untreated and recurrent urinary tract infections, including putrefaction of renal function, systemic inflammation and the evolution of multidrug resistant organisms. However, UTIs, both untreated and recurrent, were associated with worse renal outcomes and increased systemic inflammation; and recurrent UTI was associated with multidrug resistance. CRP, NGAL, IL-6, and TNF- α , as well as other key biomarkers, were all good predictors of renal dysfunction and antibiotic resistance, which could serve as potential clinical tools for early intervention. UTIs are a major problem and need prompt and appropriate management to prevent long term complications and resistance to antibiotics.

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Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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