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Evaluation of Serum Secretory Leukocyte Protease Inhibitor as a Biomarker for The Diagnosis of UTI in Women

A Thesis

Submitted to the Council of the
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In Partial Fulfillment of the Requirements for the Degree of Master Degree in Clinical Laboratories

by
(Saja Hadi Abdul Hamza)

B.Sc. in Clinical Laboratories /Applied Medical Sciences-University of Kerbala, 2019

Supervised by
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2025 A.D **1446 A.H**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

{وَمَا تَوْفِيقِي إِلَّا بِاللَّهِ عَلَيْهِ تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ }

صدق الله العلي العظيم

(سورة هود , اية 88)

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We, the examining committee, certify that we have read the thesis entitled **Evaluation of Serum Secretory Leukocyte Protease Inhibitor as a Biomarker for The Diagnosis of UTI in Women** " and have examined the student **(Saja Hadi Abdul Hamza)** in its content and that in our opinion it is accepted as a thesis for degree of Master of **Clinical Laboratories.**

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Dedication

To Allah, the Almighty, by whose grace and guidance good deeds are accomplished. To Him I raise my thanks and praise for the patience, strength, and knowledge He has bestowed upon me.

To the one whose reappearance will fill the earth with justice and equity, to the vicegerent of Allah on earth, our Master, Imam Al-Mahdi (may Allah hasten his reappearance).

And to the soul of my beloved father, who departed from this world in body, yet remains in my heart as a lasting memory, a prayer, and an unforgettable presence.

To the one beneath whose feet lies Paradise, who eased my hardships with her prayers and has been the source of my strength and success….. my mother.

To the support on whom I lean, you have always stood by my side throughout life's journey. With all my heart, I extend my deepest gratitude… my dear brothers and sister.

Saja, 2025

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With sincere thanks, Saja

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Table of Abbreviations

Abbreviations	Description
ABU	Asymptomatic Bacteriuria.
AKI	Acute Kidney Injury
AMP	Antimicrobial peptides.
ANOVA	Analysis of Variance.
AUC	Area Under Curve.
BMI	Body Mass Index.
CFU	Colony Forming Unit.
CoNS	Coagulase-Negative *Staphylococcus.*
cUTI	Complicated Urinary Tract Infection.
DM	Diabetes Mellites.
E. coli	*Escherichia Coli.*
E. faecalis	*Enterococci Faecalis.*
E. faecium	*Enterococci Faecium.*
ELISA	Enzyme Linked Immunosorbent Assay.
fimH	type 1 fimbriae.
GBS	Group B *Streptococcus*.
GUE	General Urine Examination.
HPF	High Power Failed.
HRP	Horseradish Peroxidase.
K. pneumoniae	*Klebsiella Pneumoniae*
MCA	MacConkey Agar.
NETs	Neutrophil Extracellular Traps.
NPV	Negative Predictive Value
P. aeruginosa	*Pseudomonas Aeruginosa.*
P. mirabilis	*Protus Mirabilis.*
PEDP	Pus Epithelial Dual Presence
PPV	Positive Predictive Value
RBC	Red Blood Cell.
ROC	Receiver Operating Characteristics.
rUTI	Recurrent Urinary Tract Infection.
S. aureus	*Staphylococcus Aureus.*
S. epidermidis	*Staphylococcus Epidermidis.*
S. saprophyticus	*Staphylococcus Saprophyticus.*
SD	Standard Deviation.
SE	Standard Error.
SLPI	Secretory Leukocyte Protease Inhibitor.
SPSS	Statistical Package for the Social Sciences.
SUC	Standard urine culture.
Th2	T-Helper Cell.
UPEC	Uropathogenic *Escherichia Coli.*
UTI	Urinary Tract Infection.
uUTI	Uncomplicated Urinary Tract Infection.
WHO	World Health Organization.

Summary

Urinary tract infections (UTIs) are an increasingly significant global public health issue which lead to substantial healthcare costs and negatively impacting the quality of life for patients worldwide. Thus, there is increasing demand in developing more reliable biomarkers to improve UTI diagnosis.

Secretory leukocyte protease inhibitor (SLPI) is a serine protease inhibitor with anti-inflammatory and antimicrobial activities. It has been documented that SLPI has important role during UTI. However, the importance of SLPI as potential biomarkers for UTIs diagnosis still needs further investigation.

A case-control study design was conducted. The study included one hundred and forty women with age ranged between (18 to over than 58) years classified to 70 patients with UTI and 70 apparently healthy women as a control. The age and residency were matched between the two groups. Both urine and blood samples were collected from September 2024 to December 2024 at the Urology Consultant Clinic in Imam Hussein Teaching Hospital, in the holy city of Karbala. Urine samples were used for general urine examination, bacteriological urine culture, while blood samples were used to measure the levels of SLPI using the ELISA technique.

The mean age of both groups was (39.36±14.28) and (39.10±14.38), respectively. The higher frequency of UTI patients and healthy groups were in the age category 18-37 years. Regarding the menarche status, 50 (71.4%) and 58 (82.9%) of both groups were in the reproductive state. The current study revealed that the mean ± standard division (SD) of body mass index in UTI patients' subgroups was (26.99±0.75 and 30.09±0.89) and in healthy participant subgroups was (30.40± 1.34 and 28.57± 0.87). About 59 (84.3%) of UTI patients had recurrent UTI (rUTI), whereas 26 (37.1%) of healthy control had rUTI.

Based on general urine examination (GUE), there was a significant difference among the two groups based on the presence of pus cells. Based on the presence of significant bacterial growth in urine culture, 40 (57.1%) and 28 (40.0%) for patients and control had bacterial growth. *Escherichia coli* (*E. coli*) was the most common pathogen in both UTI patients (52.5%) and Asymptomatic Bacteriuria (ABU) (46.4%) cases followed by *Staphylococcus saprophyticus* (*S. saprophyticus*) (32.5% and 32.1%) and *Staphylococcus epidermidis* (*S. epidermidis*) (10.0% and 14.3%), respectively.

Non-significant difference was found in serum SLPI between patients and control. Higher SLPI levels were observed in healthy females aged 18–37 and those who were overweight. Among healthy females, SLPI levels were significantly elevated during the reproductive phase. Regarding the clinical data of patients, higher mean level was seen in patients with rUTI, presence of urgency, absence of suprapubic pain, continence urination, absence of hypertension, and unused of antibiotics. Based to dipstick findings, there was a significant difference in SLPI level between the two studied groups according to pH categories and also within control group. There were no significant differences ($P > 0.05$) in the mean level of SLPI between the studied groups according to GUE.

Notably, the highest mean SLPI levels were associated with *S. epidermidis* in UTI patients and with *E. coli* in ABU cases. The mean of SLPI was significantly higher in healthy control, ($P = 0.014$) than patients with UTI whom they had four positive test results (Four positives meaning the participant had elevated variables like pH, pus cells (normal range less than 5 cell/HPF), Red Blood Cell (normal range less than 2-3 cell/HPF) (RBC), epithelial cell, and the bacteria was observed microscopically). Approximately 25 (58.1%) of both patients and control had culture negative and positive rUTI and SLPI in third quartile (Q3). This may indicate that

the elevated SLPI levels are either a response to recurrent infections, potentially inhibiting bacterial growth and leading to negative culture results, or a result of a persistent inflammatory response requiring increased SLPI production. Moreover, the results revealed that the area under curve (AUC) for PH, pus cells, RBC, pus/ epithelial cells dual presences (PEDP), SLPI, and epithelial cell were (0.737), (0.626), (0.632), (0.648), (0.542) and (0.518), separately. The SLPI had lower discrimination ability to detect UTI while pH value had the highest power in discrimination of UTI patients and healthy individuals.

In conclusion, (57.1%) of UTI patients had positive urine culture, whereas (40%) of healthy control had ABU. The history of rUTI was significant difference between patients and control, higher frequency was found in UTI patients. The color and appearance of urine did not differ between patients and control and this might possible reflect the useless of these parameters in UTI diagnosis. However, turbidity of urine might be useful. *E. coli* and *S. saprophyticus* had the highest frequency among bacteria isolated from urine samples.

There was no difference in the serum SLPI level between UTI patients and control group which might possibly reflect that SLPI level did not change during lower UTI unless became systemic infection or it might be associated with pyelonephritis only. On the other hand, the lack of SLPI or its presence in low level reflected the importance of SLPI in innate immune response and defending against bacterial infection and increase host susceptibility to infection. Higher mean of SLPI was found in younger people. The SLPI had poor prognostic ability to detect UTI. No significant correlation was found between the SLPI mean level and the tested parameters within urinalysis. PH value had the highest power in discrimination of UTI patients and healthy individuals. Followed by RBC, and Pus cells. PEDP had higher AUC than pus cell alone.

Chapter One

Introduction

1.1. Introduction:

Urinary tract infections (UTIs) are among the most common infections encountered in clinical settings globally. UTIs create significant clinical and economic burdens on healthcare systems and negatively impact various aspects of quality of life (Öztürk & Murt, 2020). UTIs can occur in individuals of both sexes and all ages, but females are generally more prone to these infections than males. This increased susceptibility is primarily attributed to physiological and anatomical differences in the structure of the urinary system between the sexes (Walsh & Collyns, 2017).

UTIs are classified into two categories: uncomplicated and complicated. An uncomplicated UTI (uUTI) occurs in an otherwise healthy individual and is effectively treated with a course of antibiotics. However, increasing antibiotic resistance among uropathogens has made UTI treatment more challenging. A complicated UTI (cUTI) often occurs in patients with catheters, urinary tract abnormalities, or immunological disorders (Bjerklund Johansen *et al.,* 2024).

The global prevalence of UTIs was estimated at (404.61) million cases, with approximately (236,790) deaths reported in 2019 (Yang *et al.,* 2022a). The worldwide cost of diagnosing and treating UTIs amounts to several billion dollars each year, with annual expenses in the United States estimated at approximately $2 billion (Anger *et al.,* 2019). Empirical treatment for UTIs is typically guided by the classic symptoms, such as burning sensation during urination, increased urgency, and frequent urination. Alternatively, patients may initially undergo screening procedures like urinalysis or diagnostic tests such as urine culture, with antibiotic therapy initiated based on the results or while awaiting confirmation (Wang & LaSala, 2021).

In Iraq, there were high numbers of patients infected with UTI annually caused by many types of pathogenic bacteria (Mohamed & Aljanaby, 2020). In a study conducted in Babylon governorate, the prevalence rate of UTIs among female was (36.0%) (Al-Musawi & Al-Husseini, 2021). Other study conducted in Baghdad Teaching Hospital, from December 2023 to the end of February 2024, the prevalence of UTI was found to be (31%) (Mohamed & Nassir, 2025).

Regarding diagnosis of UTI, there was no single specific test for diagnosis. Instead, the diagnosis should be made using a combination of the symptom assessment (although not specific to UTI and can occur in other condition like vaginitis, urethritis, ...etc.) and urine diagnostic methods which include urine dipsticks, microscopic examination and laboratory culture which remains the gold standard for UTI diagnosis (Kaufman *et al.,* 2019). However, false negative and false positive test results were common (in dipstick and urinalysis) and culturing of urine requires more than 24 hours which also give false negative results due to prior antibiotic usage and that infection with low count bacteria may be missed.

Additionally, the presence of a urinary microbiome and the high prevalence of asymptomatic bacteriuria underscore the need to develop diagnostic tests that can detect urinary tract inflammation in symptomatic UTI patients with high sensitivity and specificity. Due to these limitations, there is increasing interest in developing more reliable biomarkers to improve UTI diagnosis, especially in case that do not meet current diagnosis criteria (Davenport *et al.,* 2017).

Secretory Leukocyte Protease Inhibitor (SLPI) is a ~11.7 kDa non-glycosylated cationic protein (Zakrzewicz *et al.,* 2019). It is secreted by epithelial cells and is present in mucosal secretions (Maffía *et al.,* 2018). SLPI is released by host defense cells in response to inflammation, such as that caused by UTIs. It helps regulate the immune response, preventing excessive activation and thereby playing

a protective role in UTI-associated inflammation (Mongkolpathumrat *et al.,* 2024). SLPI has been documented to have important role during UTI and directly suppresses the growth of uropathogens such as *Escherichia Coli* (*E.coli*) by reducing their mRNA expression and protein production (Matsuba *et al.,* 2017). However, the potential use of SLPI as a diagnostic biomarker and whether its expression varied according to the type of bacterial isolates still need more investigation.

There are some limitations to measure SLPI in urine because urinary peptide (such as SLPI) levels can vary widely based on factors such as hydration, dietary intake, and daily cycles, which may result in inconsistent findings (Hui *et al.,* 2017). Also, urine contains a diverse mixture of proteins and metabolites that can interfere the detection of SLPI, complicating their accurate isolation and characterization (Latosinska *et al.,* 2021). SLPI can be degraded by urinary proteases which may contribute to the persistence and recurrence of UTIs by weakening the host's capacity to effectively eliminate infections (Josephs-Spaulding *et al.,* 2021).

Thus, urine assays for detecting SLPI may be less sensitive than plasma-based measurements. For example, SLPI levels in plasma have been found to correlate with the severity of bloodstream infections, indicating that plasma could offer a more dependable indicator (Lange *et al.,* 2019a). Urinary SLPI levels might not accurately represent systemic concentrations, especially in cases where SLPI is generated in response to localized inflammation or infection (Ambrosi *et al.,* 2017). Thus, it's important to study the importance of SLPI as a diagnostic biomarker for UTI.

1.2. The Aims of Study

The study aims at evaluation the role of SLPI in UTIs and determining whether it may be used as biomarker for the diagnosis of UTI by achieving the following objectives:

1. Comparison of SLPI levels between matched females with and without UTI.
2. Evaluation of SLPI as a biomarker for diagnosis or follow-up.
3. Correlation of SLPI with the severity or frequency of infection.
4. Study the effect of individual factors (like age, BMI, educational status, marital status, menarche status, hygienic practice, etc..).

Chapter Two

Literature Review

Chapter Two: Literatures Review

2.1. Definition of Urinary Tract Infection

urinary tract infection (UTI) is a comprehensive term that includes a range of infectious disorders that impact the urinary tract system (Al Lawati *et al.,*2024). The urinary system comprises the kidneys, ureters, bladder, and urethra, and its primary role is to purify blood by eliminating excess water and waste products (Mancuso *et al.,*2023). The urine of healthy individuals is sterile (Balhara *et al.,* 2023).

The disease burden in older individuals generally rises with age, and the annual growth tendency is more pronounced in those over 60 years old (Yang *et al.,* 2022a). UTI is mostly caused by microorganisms that originate in the digestive tract (Czajkowski *et al.,* 2021).

UTIs are caused by a range of pathogens, but most commonly by *E.coli, K. pneumoniae, P. aeruginosa, Enterococcus* species, and coagulase-negative *staphylococcus* (CoNS) (Shahzad *et al.,* 2022). To successfully colonize in the host and cause a UTI, uropathogens must resist the mechanical force of urine flow and evade the host's innate and adaptive immune defenses (Ko *et al.,* 2019). The majority of UTIs start when uropathogens enter the urinary tract through the urinary meatus and travel up the urethra into the bladder (Klein & Hultgren, 2020).

The significant prevalence of UTI along with the rise in antimicrobial resistance and ineffectiveness of antibiotic treatments, illustrate the critical necessity of finding alternative methods for UTI management (Sarshar *et al.,* 2020).

2.2. Epidemiology of UTI

UTIs are prevalent worldwide, exerting both direct and indirect social and economic impacts (Folliero *et al.,*2020). It has been documented that nearly three- millions of UTI-related hospitalizations in the United State were identified with a total cost exceeding $45 billion (Zilberberg *et al.,* 2022). About 30% of individuals with UTIs eventually develop a recurrence, and around 3% suffer from frequent recurrences, significantly impacting their quality of life (Wagenlehner *et al.,* 2018). The high rates of recurrence and antibiotic resistance associated with UTIs can cause substantial morbidity, particularly in healthy females (de Llano *et al.,*2020). Furthermore, UTIs are the most common infections among hospitalized patients, particularly in urology units (Hernández-Hernández *et al.,*2022).

Global prevalence of UTIs in the elderly persons was (23.6%). The highest frequency of UTIs among older individuals was observed in the following subgroups: (30%) in Africa, (30%) in women than men, diagnosis via urine culture (25.3%), and nursing home residents (47.2%) (Kalhori *et al.,*2024). The number of deaths and age-standardized mortality rate for UTIs were (17.83) times greater (Zhu *et al.,*2021).

2.3. Classification of UTI

Different classification of UTIs can be made based on the anatomical site of the bacterial infections. When the infection affects the upper part of the urinary system and presents with severe symptoms such as stomach pain, fever, chills, they are characterized as pyelonephritis and chronic kidney infection. UTIs that affect only the lower urinary tract, urethra, and bladder are categorized as cystitis and urethritis, as shown in Figure (2.1). These

infections are characterized by mild symptoms such as dysuria and hematuria (de Llano *et al.,*2020).

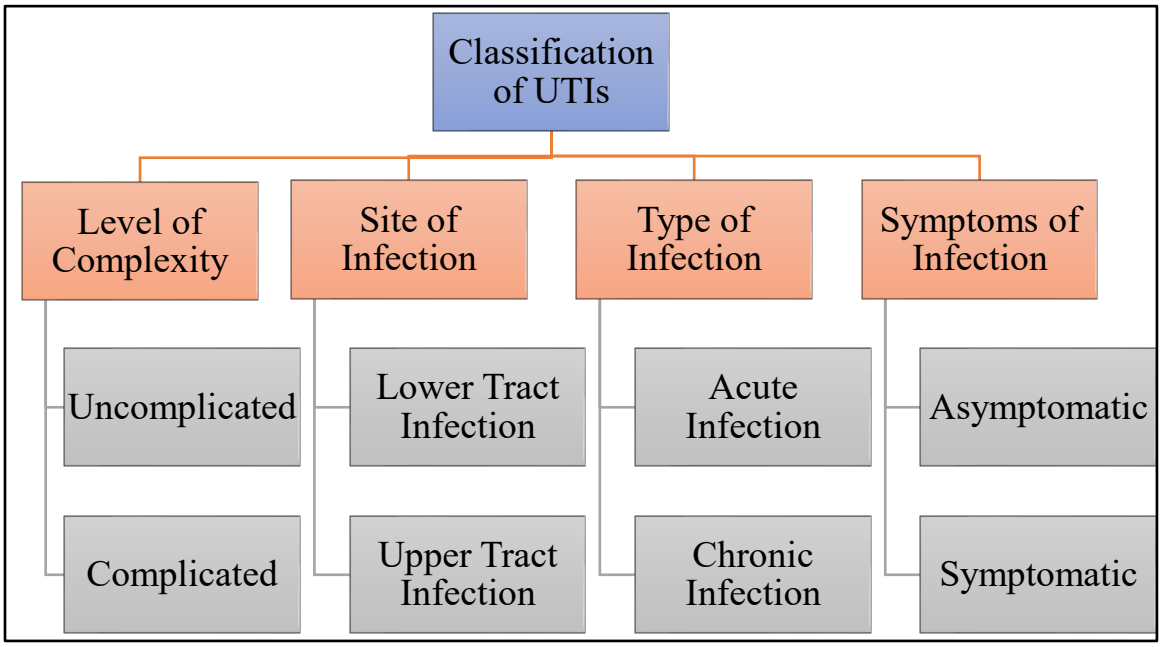


Figure (2.1): Classification of UTIs on The Basis of Different Parameters (Devi *et al.*, 2021).

2.3.1. Uncomplicated UTI (uUTI)

It is among the most prevalent illnesses addressed in primary healthcare. The clinical diagnosis of uUTI primarily relies on the patient's medical history. Typical lower urinary tract symptoms include dysuria, frequent urination in small amounts, urinary urgency. uUTIs are frequently self-limiting (Kornfält Isberg *et al.*, 2021). uUTI is characterized by sporadic or recurring cystitis in non-pregnant women without significant structural abnormalities of the urinary system (McCallin *et al.,* 2023).

2.3.2. Complicated UTI (cUTI)

It arises in individuals with structural abnormalities or underlying disorders. Therefore, raising the risk of advancing to a severe infection such as acute and/or chronic renal failure, and even urosepsis, this condition needs extended antibiotic therapies (Guerriero *et al.,* 2025). The development and management of cUTIs are mostly influenced by host characteristics rather than individual pathogen properties (Wagenlehner *et al.,*2020).

The cUTI , particularly acute pyelonephritis, accounts for a minimum of 600,000 hospital admissions annually in the United States, involving substantial healthcare expenses (Tabak *et al.,* 2019).

2.4. Risk Factor of UTI

2.4.1. Age and Sex

UTI is a significant common problem in elderly population (Zeng *et al.,* 2020). Individuals aged 65 years and older are at a higher chance for getting UTI due to many intrinsic and extrinsic risk factors, and they delay seeking medical care (Gajdács *et al.,* 2021). In results found in previous study, the elderly are more at risk for UTI due to the utilization of urinary instruments, the common occurrence of asymptomatic bacteriuria, and the presence of remaining urine (Yang *et al.,* 2022b). Women are much more prone to UTIs than men, mainly due to the female lower urinary tract anatomy and its proximity to the reproductive organs (Huang *et al.,* 2022).

Previous study indicates that roughly 15% of males and 50% of females will develop a UTI at least once in their lifetime (Medina & Castillo-Pino, 2019a; Tajbakhsh & Firoozeh, 2020). In patients with recurrent UTIs, over 80% of women indicated a return to their pre-infection clinical status,

while approximately 30% progressed from symptomatic UTIs to asymptomatic bacteriuria (Rodriguez-Mañas, 2020).

2.4.2. Hormonal Factors

Sex hormones, sex chromosomes, sexual dimorphism, and gender differences all contribute to how an organism will respond to UTI. The frequency of UTI is significantly gender-biased; however, infection rates fluctuate over the lifespan of both women and men, indicating that variations in sex hormone levels may influence the response to infection (Deltourbe *et al.,* 2022). Furthermore, the estrogen deficiency after menopause may cause atrophic changes of the urogenital tract as well as various urinary symptoms (Bodner-Adler *et al.,* 2020). Sex steroid hormones can modulate the immune system, and fluctuations in their levels throughout life affect how the host body becomes susceptible to and responds to infectious diseases.(Dias *et al.,*2022).

2.4.3. Obesity

Obesity defined as an increase in body fat leads to adipose tissue malfunction and abnormal physical forces associated with fat mass, resulting in detrimental metabolic, biomechanical, and psychological health effects (Obesity & Bays, 2019). Numerous studies have demonstrated a correlation between body mass index (BMI) and an elevated risk of infections (Dobner & Kaser, 2018). Individuals with obesity are more susceptible to developing UTI. The susceptibility to infections increased to (13%) in obese patients. The mechanisms contributing to the increased susceptibility to many infections in individuals with obesity remain poorly defined (Pugliese *et al.,* 2022).Moreover, infections in individuals with obesity exhibit a worse

prognosis, frequently prolonging the duration of hospitalization (Muscogiuri *et al.,* 2021).

2.4.4. Patient with Catheter

Catheters are widely used medical devices, but they are well known for their high risk of causing infections. Regardless of whether they are used for a short or long period, infection remains the primary concern associated with their use (Cortese *et al.,* 2018). Annually, it is projected that over 200,000 urinary catheters are inserted, leading to both infectious and non-infectious problems, elevated morbidity and death, and increased medical expenses (Schweiger *et al.,* 2020).

One mechanism of catheter-associated UTI is that catheterization triggers a strong immune response, leading to the accumulation of fibrinogen on the catheter surface. This creates an ideal environment for uropathogens with fibrinogen-binding proteins to attach and proliferate (Werneburg, 2022). Reducing the utilization of indwelling devices and discontinuing catheterization at the earliest medically appropriate time are the two primary prevention strategies for bacteriuria and infection when device usage is required (Rubi *et al.,* 2022).

2.4.5. The Urolithiasis

The UTI can develop when urolithiasis causes urine stasis, which in turn allows bacteria to attach to the urothelium and progress (Choe *et al.,* 2018). Urolithiasis is defined as the presence of any stone in the urinary system identified using imaging techniques such as ultrasonography and computed tomography. The prevalence of urolithiasis correlated with worse clinical outcomes in UTI patients, including elevated risks of bacteremia, urosepsis shock, and acute kidney injury (Hsiao *et al.,* 2019). A previous study

reported that the prevalence of urolithiasis among patients with UTIs was 17.2% (Hsiao *et al.,* 2021).

2.4.6. Diabetes Mellitus (DM)

UTI represents a significant problem for those with DM. Both type 1 and type 2 DM elevate the incidence of UTIs and bacteriuria attributable to *Enterobacteriaceae*, particularly in female patients (Kamei & Yamamoto, 2021). The increased incidence of UTIs in diabetes individuals is attributed not to variations in bacterial strains but to alterations in uro-epithelial cells that enhance bacterial adhesion (Yenehun Worku *et al.,* 2021). Diabetic patients can develop dysuria as a complication of UTIs, resulting from organ damage, with potentially life-threatening diseases arising from pyelonephritis and associated renal impairment (Tegegne *et al.,* 2023). A study conducted in India found that the overall prevalence of UTIs in diabetic patients was (17.5%) (Laway *et al.,* 2021).

2.4.7. The Congenital Malformations

It mostly affects the upper urinary tract and can lead to a wide range of problems in the kidneys and ureters, from simple variations that don't have any effect on health to complex malformations that can cause major issues and end-stage renal disease (Houat *et al.,* 2021). A previous study that found the congenital anomalies of the kidney and urinary tract were more common in children, and the prevalence of UTI in these patients reached (64%) consisting of (52%) obstructive type and (12%) non-obstructive type (Ramayani *et al.,* 2018).

2.5. Pathogenesis of UTI

The majority of UTIs originate when bacteria invade the urinary tract via the urinary meatus, subsequently ascending the urethra and entering the bladder lumen. UTIs start when uropathogens colonize the urethra and subsequently the bladder through the action of specific adhesions. If the bacteria are able to evade the immune system, they begin to multiply and biofilm form. Bacteria can reach the kidney from the lower urinary tract, and UTI can evolve into bacteremia, as shown in Figure (2.2). If left untreated the UTI can progress to pyelonephritis and bacteremia (Mancuso *et al.,* 2023). The infectivity of pathogens is associated with cell-surface components and/or secreted virulence factors. Bacteria have developed complex and diverse adaptation mechanisms to the host environment, including biofilm formation, survival within professional phagocytes, and evasion of the host immune response (Lannes-Costa *et al.,*2021; Stewart, 2022).

The increasing multi-drug resistance and the capacity of these bacteria to build biofilms complicate the treatment of infections, which frequently impacts individuals with immunodeficiency or those in intensive care units (Bagińska *et al.,* 2021). If the host's inflammatory response does not eradicate all bacteria, the bacteria proliferate, generating toxins and enzymes that enhance their survival (Mancuso *et al.,*2023).

A systematic interdisciplinary study revealed a novel conceptual model of UTI, wherein the risk and outcome of UTI are influenced by a combination of dynamic host susceptibility factors and various bacterial urovirulence phenotypes, driven by both gene content variations and differential expression of conserved functions (Klein & Hultgren, 2020). The urinary tract is influenced by its contacts with other mucosal sites, such as the genitourinary and gastrointestinal systems. Each of these places contains varied microbial

ecosystems known as microbiota, which regulate complex interactions with both the local and systemic immune systems (Jones-Freeman *et al.,*2021).

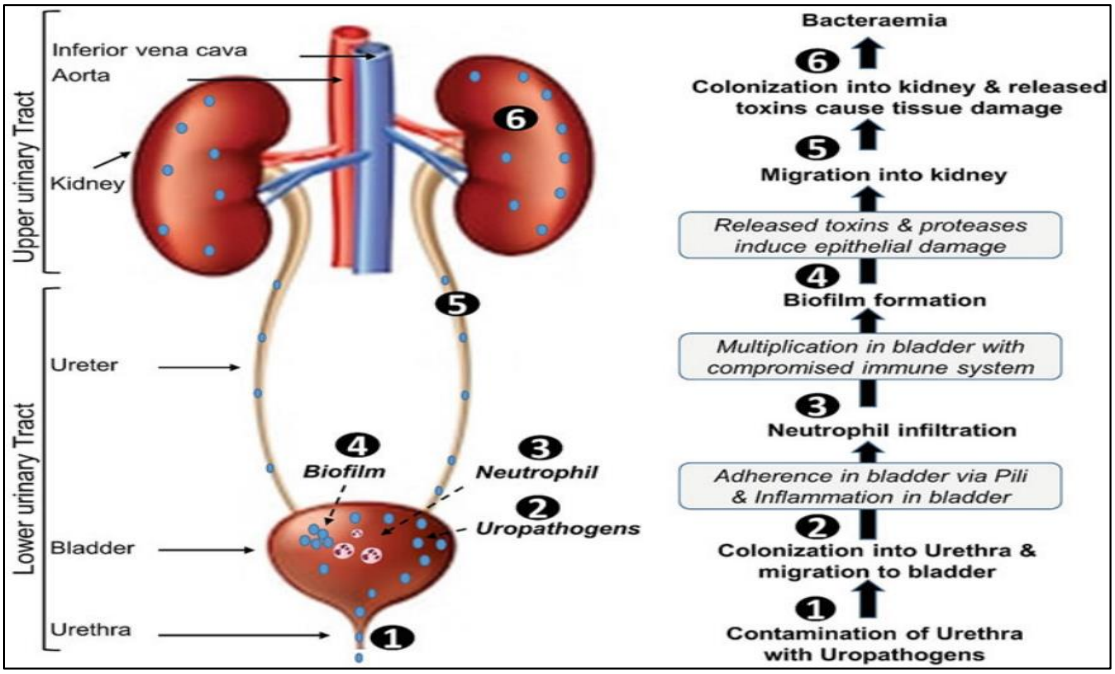


Figure (2.2): Pathogenesis of UTI (Idrees & Saeed, 2021).

2.6. Etiological Agents of UTI

Bacteria are the primary causative agents of these infections. However less frequently, other microorganisms such as fungi and some viruses have been identified as responsible for UTIs.

Uropathogens exhibited significant variations in epidemiology, species distribution, and susceptibility patterns among the many areas and populations investigated (Behzadi *et al.,*2021). The primary organism responsible for both complicated and uncomplicated UTIs is uropathogenic *E. coli* (UPEC), followed by *K. pneumoniae, S. saprophyticus, E. faecalis,* group B *Streptococcus* , and *P. mirabilis* (Zhou *et al.,* 2023). Typically, these uropathogens initiate colonization of the perineal and periurethral surfaces

prior to the onset of infection (Fazly Bazzaz *et al.,*2021), as shown in Figure (2.3).

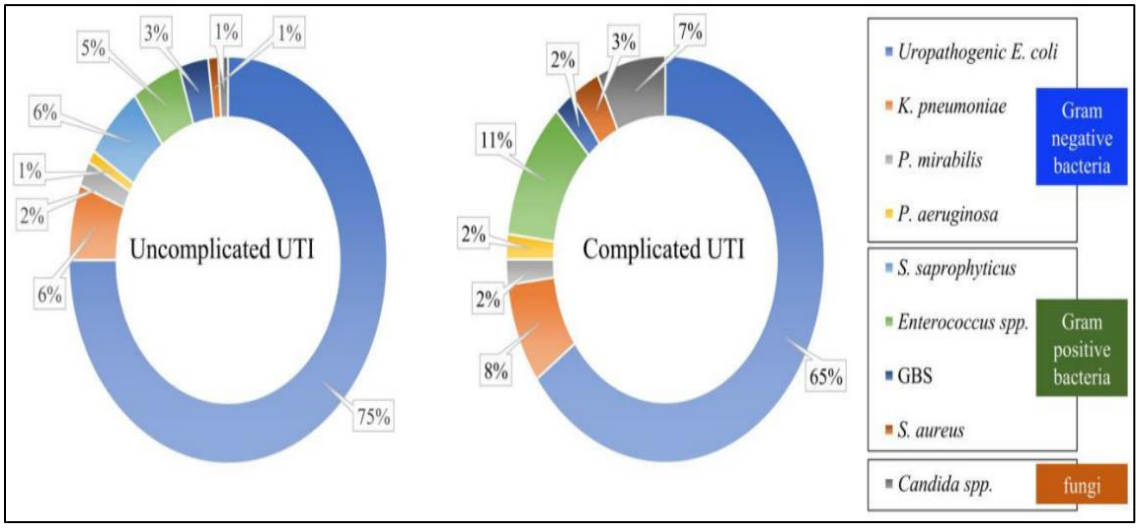


Figure (2.3): Epidemiology of UTIs (Zhou *et al.*, 2023).

2.6.1. Gram Positive Bacteria

Gram-positive facultative anaerobic cocci encompass various phenotypically diverse genera, including *Staphylococcus spp*., *Streptococcus* groups B (GBS), and *Enterococcus spp.* (group D *streptococci*) (Colaninno, 2021).

The genus *Staphylococcus* is implicated in numerous human illnesses, including toxic shock syndrome, pneumonia, endocarditis, and UTI. They are catalase-producing, Gram-positive spherical cocci resembling grapes. The most clinically significant species of this genus include *S. aureus, S. epidermidis and S. saprophyticus* (Assoni *et al.,*2020).

S. aureus is present in the environment and is also part of the normal human flora, residing on the skin and mucous membranes (Taylor & Unakal, 2023). *S. aureus* is a prevalent global source of morbidity and mortality attributed to an infectious pathogen (Cheung *et al.,*2021). The extensive

immune evasion mechanisms in *S. aureus* demonstrate the long-standing connection between the bacteria and humans, marked by chronic colonization and sporadic invasive infections (Howden *et al.,*2023). The emergence of methicillin-resistant *S. aureus* (MRSA) strains makes the pathogenicity of *S. aureus* problematic in both healthcare facilities and community environments. Since its identification in the early 1960s (Lee *et al.,* 2018). The high pathogenicity of *S. aureus* leads to recurring nosocomial and community-associated infections, making immediate isolation and identification of these strains crucial for timely care (Aubais Aljelehawy *et al.,*2021).

S. aureus causes ascending urinary tract colonization and infection, typically following *Staphylococcal* bacteremia from other sites, such as in cases of endocarditis (Selim *et al.,*2022). *S. aureus* may result in complicated UTI in certain diabetics patients who are immunosuppressed or have catheters applied (Zubair *et al.,*2019).

The CoNS in comparison to *S. aureus*, exhibit a diminished ability to induce acute, life-threatening infections. CoNS are becoming significant as microorganisms responsible for infections in immunocompromised individuals and following the implantation of foreign materials (Becker *et al.,*2020). A state of the host immune system affects the onset and outcome of CoNS disease, resulting in an unclear distinction between pathogenic and nonpathogenic CoNS (Heilmann *et al.,*2019). Consequently, they are frequently categorized as contaminants rather than the etiological agent of infection. The differentiation between infection and contamination is not always obvious, and most efforts to establish distinguishing markers have proven ineffective (Michels *et al.,*2021).

Numerous CoNS species, which represent the normal microbiota of human skin and mucosal surfaces, can also cause infections. Encompass

various medical important species including *S. epidermidis*, *S. haemolyticus*, and *S. capitis* (Foster, 2024).

The predominant CoNS populating human skin and mucous membranes is *S. epidermidis*, which is responsible for nosocomial infections (Raheema *et al.,*2020). Researchers have noted that *S. epidermidis* was the most commonly identified *Staphylococcal* species on high-touch surfaces in both community settings and hospitals in London (Cave *et al.,* 2019). A study conducted to isolate strains in UTI find that from out of 126 urine samples, 39 (30.95%) samples were positive for *S. epidermidis* (Talebi *et al.,* 2022). Another study got a similar result: the prevalence of *S. epidermidis* was 24 (36.9%) (Phillip *et al.,* 2023).

S. saprophyticus is a causative agent of UTI, particularly in young women (Michels *et al.,* 2021). Upon contaminating the periurethral region with *S. saprophyticus* from the gastrointestinal tract, the bacteria will colonies the urethra prior to ascending to the bladder. Upon detection of bacterial infection by the host immune system, phagocytes, macrophages, and neutrophils are recruited to engulf the bacteria, a phagosome then encloses the bacteria, however *S. saprophyticus* bacteria can eventually escape the digestion pocket in coating themselves with the hosts proteins (Djawadi *et al.,*2023). A previous study found that *S. saprophyticus* was a less common pathogen in cUTI, occurring at prevalence (6%) (Lila *et al.,* 2023).

Streptococcus is a significant genus including primary and opportunistic pathogens in humans and animals, as well as non-pathogenic commensals (Timoney, 2022). The genus *Streptococcus* comprises Gram-positive spherical or ovoid cells that are commonly organized in chains or pairs, which may be dispersed in the environment and/or colonize the skin and mucous membranes of both humans and animals (Stewart, 2022). *Streptococci*

constitute a diverse group of bacteria, comprising over 60 recognized species. Certain species, including *S. pyogenes* and *S. agalactiae*, produce hemolytic factors and can be classified as beta-hemolytic when grown on media containing blood (Haenni *et al.,* 2018).

Streptococcus species were initially categorized by Rebecca Lancefield, she is recognized for the classification of beta-hemolytic *streptococci*, having methodically devised a technique to distinguish human strains (group A beta-hemolytic *Streptococcus*) from those largely associated with animal diseases (Carroll, 2019).

The GBS a commensal bacterium found in the gastrointestinal and/or urogenital tract of (30–40%) of adults. GBS frequently induces various disease in susceptible populations, such as infants, pregnant and non-pregnant women and the elderly. Among these diseases are UTIs, including cystitis and pyelonephritis (Goh *et al.,* 2024). A study found that *Streptococcus spp.* was the second most common cause of community acquired-UTI, after *E. coli*. The same study also found that S. *agalactiae* was the most common type of *Streptococcus spp*. accounted for (52%) and around (9%) of the total number of patients with UTI; (92%) of women were infected with GBS (Islam *et al.,*2022).

Enterococci are Gram-positive, facultative anaerobic cocci that occur in short to medium chains, initially identified in 1899 within the human gastrointestinal system. They were identified as a distinct genus from *Streptococci* using DNA hybridization (Said *et al.,*2021). The predominant *Enterococcus* species responsible for UTIS are *E. faecalis and E. faecium*, which possess various mechanisms, including biofilm formation and virulence factors (Codelia-Anjum *et al.,* 2023). The prevalence of UTIs

caused by *Enterococcus* in the elderly is approximately (11.6%), compared to only (5.3%) in the rest of the population (Matulay *et al.,* 2016).

2.6.2. Gram Negative Bacteria

Gram-negative bacteria represent a major public health challenge globally due to their significant antibiotic resistance. These microorganisms possess considerable clinical significance in hospitals as they elevate the risk for patients in the intensive care unit, resulting in increased morbidity and mortality rates (Oliveira & Reygaert, 2019). Gram-negative bacteria including *E. coli*, *Klebsiella spp*., *Pseudomonas spp.,* and *P. mirabilis* are frequently recovered from urine samples (Alamri *et al.,* 2018).

E. coli is the most common member of the *Enterobacteriaceae* family. It is widely recognized as the leading cause of UTIs in numerous countries (Gajdács *et al.,* 2019). *E. coli* is a commensal organism of the vertebrate gastrointestinal tract that is increasingly implicated in several intestinal and extra-intestinal infections as an opportunistic pathogen (Denamur *et al.,*2021). *E. coli* is the predominant etiological agent of bacteremia in high-income nations, surpassing other major pathogens such as *S. aureus* and *S. pneumoniae* (Bonten *et al.,*2021).

Approximately 80% of uncomplicated UTIs are attributed to UPEC, which exhibit enhanced adhesion to vaginal epithelial and urothelial cells (Delcaru *et al.,* 2016). Moreover, *E. coli* can induce both community-acquired and healthcare-associated illnesses, affecting individuals across all age groups (Galindo-Méndez, 2020). Pathogenic *E. coli* bacteria have distinct mechanisms and virulence factors encoded by specific gene sets (Sciences, 2021). The transmission of UPEC can also occur through sexual contact and oral-fecal pathways (Terlizzi *et al.,* 2017). UPECs initially colonize the human host by attaching to the bladder epithelium. Adhesion is succeeded by the

bacterial invasion of urothelial epithelial cells, forming the so-called intracellular bacterial communities exhibiting biofilm-like characteristics (Conover *et al.,* 2016).

UPEC are more prone to infecting the host via the lower urinary tract. When the effects of UPEC on the body are significant, the host experiences a UTI or maybe a more severe illness (Zhou *et al.,*2023). The findings of previous study indicated that the predominant pathogenic bacterium in the urine samples of 314 hospitalized patients was *E. coli*, comprising (52.5%), followed by *Enterococcus spp*. at (22.9%), *Enterobacteriaceae* other than *E.coli* at (20.4%), *Streptococcus spp*. at (2.2%), and *Staphylococcus spp.* at (1.9%) (Shi *et al.,*2023).

K. pneumonia is a significant member of *Enterobacteriaceae* family, It is considered opportunistic organisms causing broad spectrum of infections and exhibition highly degree of resistance to antibiotics (Microbiol *et al.,*2020). *K. pneumoniae* responsible for a great variety of infectious illnesses, including UTI, bacteremia, pneumonia, and liver abscesses (Wang *et al.,*2020). In the last decade, *K. pneumonia* has appeared as a major medical and public health risk due to increasing prevalence of health-associated infections arisen by multidrug-resistance species developing wide range of β-lactamases and/or carbapenemases (Wyres *et al.,*2020). Nonetheless, additional study from Middle Eastern regions and developing countries identifies *K. pneumonia* as the primary cause of UTI (Hossain, 2023). In a prior study, the researcher examined (140) samples from persons diagnosed with UTIs. The findings indicated that (35.7%) of specimens yielded a positive culture for *K. pneumoniae* (AlObaidi *et al.,*2022).

The genus *Enterobacter* is a common cause of nosocomial infections. Previously, the predominant species were *E. cloacae* and *E. aerogenes*

(Álvarez-Marín *et al.,*2021). *E. aerogenes* has lately been reclassified as *K. aerogenes.* The phenotypic variation between *E. aerogenes* and the genus *Klebsiella* include motility, the presence of ornithine decarboxylase, and the absence of urease activity in *E. aerogenes* (Davin-Regli *et al.,*2019). These bacteria generally show a multidrug-resistant (MDR) phenotype, primarily as a result of their adaptability to the hospital environment and their capacity to acquire mobile genetic elements that harbor resistance and virulence genes. The incidence of MDR *E. aerogenes* strains in UTI is increasing *(Shantiae et al.,*2022).

P. mirabilis is a Gram-negative facultative anaerobe characterized by swarming motility and the capacity for self-elongation, in addition to the secretion of a polysaccharide that facilitates adhesion and movement along surfaces such as catheters, intravenous lines, and other medical apparatus (Jamil *et al.,*2022). To causes UTI, the *P. mirabilis* must first enter urethra. Since *P. mirabilis* is primarily found in soil and in the human gastrointestinal tract, the intermittent colonization of the area surrounding the urinary tract established by using the bacteria from gastrointestinal tract as repository (Yuan *et al.,*2021).

The frequent use of catheters and medical instruments in elderly patients increases their risk of developing UTIs caused by *P. mirabilis* (Medina & Castillo-Pino, 2019b). The risk factors for development of *Proteus*-mediated UTIs include sexual activity in both males and females. Additionally, immunocompromised status and the risk of *P. mirabilis* infections is heightened in female with prolonged catheter use, poor catheter hygiene and maintenance, pre-existing medical conditions and a lack of access to systemic antibiotic therapies (Jamil *et al.,*2023).

2.7. The Virulence Factors of Etiological Agents.

The following are the most common virulence factors for bacteria that cause UTIs:

- Adhesion Factors**:** Fimbriae, especially type 1 fimbriae (fimH), play a key role in adhering to the uroepithelial cells, which is essential for colonization and infection by bacteria such as UPEC (Salian *et al.,* 2024).
- Degradative Enzymes: like coagulase, hyaluronidase, deoxyribonuclease, and lipase which are enzymes that enhance pathogenicity and facilitate dissemination inside the host like *S. aureus* (Kayan & J., 2019). Protease enzymes can degrade defensive secretory immunoglobulins such as IgA. Uropathogenic bacteria including *E. coli*, *P. mirabilis*, *K. pneumoniae*, and *P. aeruginosa* secrete proteases that facilitate immune evasion and contribute to UTIs (Solanki *et al.,* 2021).
- Antibiotic Resistance**:** antibiotic resistance and the synthesis of bacteriocins and enterotoxins also contribute to the pathogenicity of CoNS (França *et al.,*2021). Furthermore, multidrug resistance is widespread among UPEC, with certain strains exhibiting resistance to as many as 12 antibiotics (Sung *et al.,* 2024).
- Biofilm Formation: some bacteria harbor genes that encode virulence factors linked to the a etiology of UTIs, including biofilm formation like CoNS (Phillip *et al.,*2023). The capacity of *Enterococci* to establish biofilms enhances adherence to catheters, dental prosthesis, and heart valves, while hindering antibiotic penetration, resulting in persistent infections that are frequently polymicrobial (Ch'ng *et al.,*2019).
- Toxins: exotoxin like hemolysin, a key virulence factor, plays a role in tissue damage and immune evasion and is commonly found in clinical

isolates of *Enterobacteriaceae* including *E. coli, Klebsiella species, and Proteus species* (Soujanya & Banashankari, 2023). UPEC strains employing many virulence factors including endotoxin like lipopolysaccharides, to establish pathogenicity in the urinary tract (Karam *et al.,*2019).

- Iron scavenger receptors: in UPEC are key virulence factors that enable bacteria to acquire iron from the host by binding siderophores and heme complexes. This mechanism allows UPEC to overcome nutritional immunity, supporting bacterial growth, persistence, and recurrent UTIs (Taban *et al.,* 2022).

2.8. Sing and Symptoms of UTI

The majority of UTIs are managed with empirical treatment (Johnson, 2017). The clinical manifestations of a UTI was shown in table (2.1) which include infection-related inflammation of the urethra (urethritis), urinary bladder (cystitis) and kidneys (pyelonephritis) (AL-Khikani *et al.,* 2019).

Table (2.1) Clinical Manifestations of UTI.

No	Clinical Manifestations	Sign and Symptoms
1.	Cystitis	Dysuria or pain post-micturition, frequency of urination, urgency, opaque or foul-smelling urine, and discomfort or pain in the bladder, urethra, or vagina (McKertich & Hanegbi, 2021).
2.	urethritis	Dysuria, mucopurulent urethral discharge, urethral pain, and erythema (Sell *et al.,*2021).
3.	Pyelonephritis	Inflammation of renal parenchyma resulting from bacteria ascending from bladder through ureters up to kidneys (Hudson & Mortimore, 2020). Fever, flank pain, nausea, vomiting, burning when urinating, increased frequency, and urgency (Belyayeva & Jeong, 2020).

2.9. Asymptomatic Bacteriuria (ABU)

An asymptomatic bacteriuria (ABU) is a disorder characterized by presence of bacteria in urine samples collected from patients without any signs or symptoms related to UTI (Omar, 2022). ABU is a prevalent clinical

condition, with its incidence increasing with age, and it is significantly more common in women than in men (Al Youssef *et al.,*2020). In elderly, the typical symptoms of UTI are exchange with a variety of nonspecific manifestation. Dysuria, fever, and leukocyturia are frequently absent, instead that patients exhibit other symptoms such as anorexia, cough, or confusion (Manseck *et al.,*2022). The infectious diseases society of America advised that ABU should be checked and treated solely in pregnant women or in individuals prior to invasive urologic treatments. Treatment was considered inappropriate for healthy women, older individuals, men, or those with diabetes, indwelling catheters, or spinal cord injuries (Nicolle *et al.,* 2019).

2.10. The Pathogenesis of ABU

ABU a non-specific word describing the presence of bacteria in urine, is prevalent among individuals with neuropathic bladders (Forster & Pohl, 2019). The neuropathic bladder reveals that distinct communities of microbes are present compared to people with healthy functioning bladder (Groah *et al.,* 2016)**.** Elderly often exhibit a diverse array of comorbidities, functional impairments, and cognitive deficits, rendering them more susceptible to elevated rates of ABU and UTI (Rodriguez-Mañas, 2020).

The pathophysiology of ABU may be due to the colonization of the urinary mucosa by deficient bacterial strains that are unable to trigger a complete inflammatory response (Gołębiewska *et al.,* 2023). Patients with ABU may harbor the strain of bacteria for months or years without exhibiting a disease response, allowing the commensal-like bacteria to co-evolve successfully with the host in a niche with other microbial opponents (Maniam *et al.,* 2022). The consequences of ABU encompass spontaneous resolution,

resolution by antimicrobial treatment, persistence of bacteriuria with identical or varied species, or progression to UTIs (Nicolle, 2017).

2.11. The Causative Agents of ABU

The predominant bacteria identified in urine specimens in cases of ABU are *E. coli* and various *Enterobacteriaceae*, including *Klebsiella spp.*, *Enterobacter spp.*, *Proteus spp.*, and *Citrobacter spp*. Various organisms may encompass CoNS, *S. aureus*, *Enterococcus spp.*, *S. agalactiae*, and other Gram-negative bacilli such as *Pseudomonas spp* (Blãnaru & Popa, 2024). Healthy persons are likely to harbor *E.coli*, whereas those with comorbidities, such as diabetes, and individuals with a long-term indwelling urinary catheter residing in a long-term care facility are more prone to colonization by multidrug-resistant bacteria, such as *P. aeruginosa* (Luu & Albarillo, 2022).

In a study conducted in 2019, the predominant ABU isolate was *E. coli* (30.8%), followed by *K. pneumoniae* (26.9%) and *Proteus spp.* (3.8%) (Akpan *et al.,* 2019). In Iran, a study found that *E. coli* was the most common type of bacteria in ABU (46.2%). It was followed by *S. saprophyticus* (23.1%), *Klebsiella* (15.4%), *Enterobacter* (7.7%), and *Streptococcus* group B (7.7%) (Farazi & Jabbariasl, 2019). It has been documented in a previous study that *E. coli* isolated from ABU cases exhibit a diminished number of virulence factors compared to those isolated from UTIs (Maniam *et al.,* 2023).

2.12. The Recurrent UTI (rUTI)

The rUTIs are defined as the recurrence of either complicated or uncomplicated UTIs happening three or more times annually or twice within the previous six months (Bonkat, 2021). The rUTIs are relatively common in healthy, premenopausal, sexually active women, and particularly in postmenopausal women (Hernández-Hernández *et al.,* 2022b). The rUTI may

be promoted by certain uropathogens capacity to modify their morphology, allowing them to escape the host immune system and more readily recolonize unexposed areas of the urinary tract (Murray *et al.,*2021).

A rUTI may manifest as relapsing infection due to partial eradication of the causal pathogen or as re-infection occurring after 14 days post treatment completion (Zare *et al.,* 2022). A prevalent theory about the mechanism of recurrence of UTIs suggests that the gastrointestinal tract serves as a reservoir for uropathogens, which are regularly reintroduced into the urinary tract through contamination of the periurethral surface and subsequent retrograde ascent (Murray *et al.,* 2021). In rUTI, non-antibiotic prophylaxis is advised as the primary treatment, focusing on behavioral treatments and immune system regulation (Czajkowski *et al.,* 2021).

2.13. Diagnostic Methods of UTI

Urine is a body fluid easily obtainable for medical assessment in patients. Urine test is a non-invasive procedure that causes no pain or discomfort for patients and is utilized to assess renal function disorders (Aitekenov *et al.,*2021).

2.13.1. General Urine Examination (GUE)

It is crucial for all patients with kidney-related diseases. Urinalysis can involve physical, chemical or microscopic tests. Microscopic assesses criteria including red blood cell (RBC), white blood cell (WBC), epithelial cells, crystals, bacteria and casts. The test results indicate several renal disorders including hematuria and kidney stones (Suhail & Brindha, 2021).

2.13.1.1. Macroscopic Examination

The macroscopic examination of samples is frequently essential for precise histopathological reporting. However, it has typically been ignored and may be assigned to untrained personnel with minimal oversight and

direction (Varma & Dormer, 2024). Urine can be visually evaluated, facilitating rapid assessments of diseases identification through macroscopic alterations in urine, including variations in foam appearance, turbidity, and sediment presence *(*Zhang *et al.,*2022).

2.13.1.2. Dipstick Test

Dipsticks are readily accessible, cost-effective and yielded quick findings. In certain areas, they are commonly utilized in conjunction with symptom (Wagenlehner *et al.,*2022). Dipstick/dry chemistry analysis is applying urine to various sections of a dipstick, permitting a timed response and subsequently compering the resultant color change to reference standard to determine the result as either positive or negative (Kavuru *et al.,*2020a).

Parameters RBC, protein and pH may improve the UTI dipstick test (Fan & Bai, 2020). It is Simple, cost-effective tests (visual examination of color and turbidity, odor identification, specific gravity measurement, and analysis of essential chemical constituents) are possible and frequently conducted by physicians and trained healthcare professionals in point-of-care environments (clinics and hospitals) (Kavuru *et al.,* 2020b). A published study indicated that (61%) of individuals with positive dipstick urinalysis exhibited negative urine culture results. It indicates low sensitivity and elevated specificity for dipstick urinalysis (Chu & Lowder, 2018).

2.13.1.3. Microscopic Examination

The microscopic examination of urine sediment is increasingly seen as a diminishing skill among clinicians. Urine examination can offer valuable insights. Careful observation of urinary cell morphology, identification of both cellular and non-cellular casts, detection of different endogenous and drug -related crystals can facilitate a quick diagnosis of acute and chronic

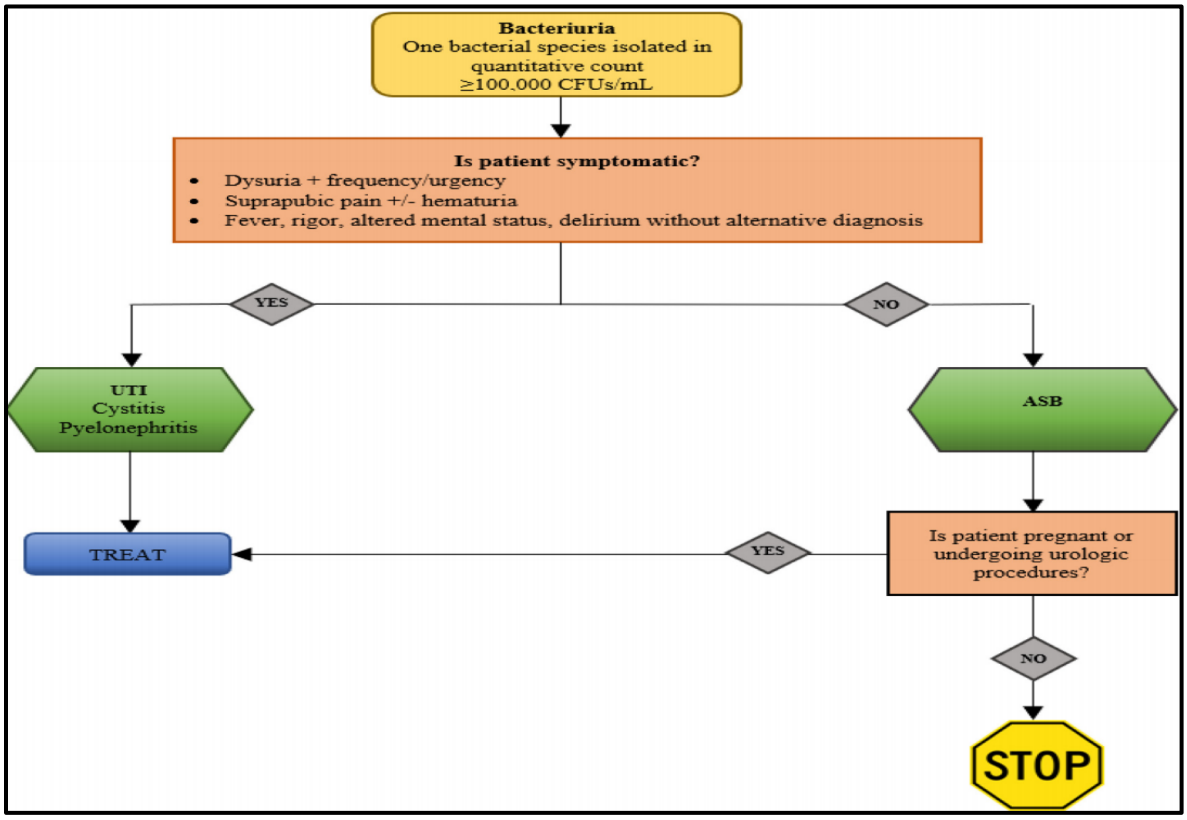
kidney disease (Cavanaugh & Perazella, 2019). Samples containing 2–3 pus cells/HPF and 2–3 epithelial cells/HPF were classified as negative for UTI, while samples with 4–10 pus cells/HPF and 10–20 epithelial cells/HPF were classified as positive for UTI (Kaur *et al.,*2020).

A prior study utilized microscopic analysis for the diagnosis of UTI, yielding a sensitivity of 55% and a specificity of 88% for this method (Chaudhari *et al.,* 2018). The microscopic examination of urine has become a standard diagnostic procedure in modern hospitals across all stages, evolving into advanced microscopic technologies and digital platforms (Zhang *et al.,* 2022). The primary issue with this method is time consumption and the potential for manual errors. A highly trained technician is required to perform the analysis. Manual microscopy elevates worker costs and is less practical for high-volume laboratories (Suhail & Brindha, 2021).

2.13.2. Urine Culture

Standard urine culture (SUC) is currently the gold standard for diagnosing UTI (Karah *et al.,*2020). A positive urine culture in individuals absent from genitourinary tract symptoms is prevalent in many groups especially elderly, hospitalization or any underlaying conditions (Nicolle *et al.,*2019). A culture became positive if a substantial increase ($\geq 10^4$ colony-forming units (CFU)/mL) of one or two bacteria was seen. Cultures exhibiting three or more bacteria were classified as contamination (Zboromyrska *et al.,*2022). A study revealed that the sensitivity of SUC in identifying patients with UTI is relatively low, at around (16.7%) (Yoo *et al.,*2021). Urine culture is necessary to confirm or ruled out a UTI only when the result of urinalysis such as in dipstick or microscopic examination abnormal, unless neutropenic patients (Laan *et al.,*2021).

The specificity of urine cultures significantly differs among populations, ranging from 0% to 90%. This diversity in specificity arises biologically from distinct populations characteristics that promote chronic bacterial colonization, resulting in false-positive outcomes in asymptomatic individuals (Chan-Tack *et al.,* 2020). The problem with this method is that the overall turnaround time is long, which takes 48–72 hours for the final report (Pirkani *et al.,*2020). Figure (2.4) was constructed to help clinicians identify and treat asymptomatic bacteriuria when indicated.



*ASB; Asymptomatic Bacteriuria, UTI; Urinary Tract Infection, CFU; Colony Forming Unit.

Figure (2.4): Clinical Approach to Management of Asymptomatic Bacteriuria (Luu & Albarillo, 2022).

2.14. Body Defenses Against UTI

2.14.1. Inflammatory Response in UTI

Inflammation is fundamental aspect of life in mammals. It offers essential protection against detrimental environmental effects by maintaining homeostasis and preserving the functional and structural integrity of tissues and organs (Medzhitov, 2021). Metabolic and neuroendocrine alterations may arise based on the severity and scope of the inflammatory response, whether systemic or localized, to preserve metabolic energy and transfer additional nutrients to the activated immune system (Furman *et al.,*2019). Inflammation is triggered either by significant variations in homeostatic variables or by tissue injury resulting from the disruption of homeostasis (Meizlish *et al.,*2021). Intact skin and mucosal barriers are essential for maintaining tissue homeostasis, as they protect host tissues from infections, environmental toxins, pollutants and allergens (Akdis, 2021). The five fundamental signs of inflammation include heat, redness, swelling, pain and loss of function (Hannoodee & Nasuruddin, 2020).

The bladder is constantly covered by passive defenses, including a mucus layer, antimicrobial peptides, and secretory immunoglobulins; nonetheless, these defenses can be periodically disrupted by invading pathogens that provoke an effective host inflammatory response in the bladder. The urothelium and resident immune cells generate extra defense chemicals, cytokines, and chemokines that attract inflammatory cells to the affected area (Lacerda Mariano & Ingersoll, 2020). In addition to pathogen virulence factors, the body has several physiological defenses against the development of ascending infections. Firstly, the urethra acts as a barrier to prevent bacteria from reaching the bladder. Secondly, the act of urination helps flush out the majority of the bacterial population (Loubet *et al.,*2020).

2.14.2. Stages of Immune Response in UTI

The urinary system is continuously exposed to many pathogens that inhabit the GIT and it is often efficient to fight infections caused by these pathogens. The resistance to infection is mostly achieved by the adaptability of the immune system in the urinary tract, involving both innate and adaptive immunity. In all immune responses, the stimulus-dependent components of the immune system in urinary tract must maintain a balance between response efficacy and excessive inflammation (Martell, 2020).

Urothelial cells have several distinct modifications to inhibit the invasion of bacteria migrating from the gastrointestinal system. The uroplakin plaques generated by the urothelium provide a physical barrier against bacteria (Bowyer *et al.,*2022).

The two principal components of this defensive system are innate and adaptive immunity. Both are represented by specific cells that eliminate danger either directly (cell-to-cell) or indirectly (via mediators). Immune responses are complex and distinct, and the mechanisms function in various illnesses remain inadequately understood (Matejuk *et al.,*2021).

2.14.2.1. Innate Immunity

The innate immune system serves as the primary line of defense for the host against infections. Innate immunity restricts pathogen entrance, translation, replication and assembly, facilitate the identification and elimination of infected cells, and regulate and accelerate the development of adaptive immunity (Diamond & Kanneganti, 2022). Innate immunity comprises a cellular component and a humoral component. The biological mechanisms employed to detect microbial components and tissue injury utilize cell-associated pattern-recognition receptors, such as toll-like receptors (Mantovani & Garlanda, 2023). Dysregulation and hyperactivation of the

innate immune system can lead to acute and chronic inflammatory diseases associated with considerable morbidity and mortality (Place & Kanneganti, 2020).

The innate immune system utilizes two distinct strategies to identify pathogens: firstly, it recognizes microbial components as ligands for pattern recognition receptors and secondly, it detects the actions of pathogen-encoded effectors (Hornung & Gaidt, 2024). The urinary bladder has many innate immune cells, such as macrophages, dendritic cells, and mast cells, which serve protective functions. Furthermore, bladder epithelial cells contribute to innate immune actions. When tissue-resident cells are inadequate, the body recruit's non-resident immune effector cells from the bloodstream, such as neutrophils and monocytes. These diverse immune cells emphasizing the dynamic characteristics of urinary tract defense systems (Naskar & Choi, 2024).

Despite the host eliciting a strong innate immune response to eliminate both extracellular and intracellular bacteria in the bladder, the elevated incidence and recurrence rates indicate that the adaptive immune system in the bladder is insufficient in managing the invading bacteria (Wu & Abraham, 2021).

2.14.2.2. Adaptive Immunity

The adaptive immune system and related inflammation are essential for monitoring and safeguarding the host against internal and external dangers, although they can accidentally damage host tissues. The cells responsible for adaptive immune responses are termed lymphocytes, which are categorized into B-lymphocytes and T-lymphocytes (DeMaio *et al.,*2022). Study conducted on the bladder's adaptive immune report that, upon bacterial infection, the bladder initiates an extensive T-cell response with a pronounced

Th2 bias, which is further amplified during recurrent infections. The Th2-mediated immune response concentrates on restoring the superficial bladder epithelium after infection-induced exfoliation of this barrier (Wu *et al.,*2020). A consequence of a significant Th2 response is the suppression of the bacteria-clearing Th1 response in hosts with a history of recurrence UTIs, thereby raising their susceptibility to reinfections (Wu *et al.,*2021).

The adaptive immunity responds more slowly but can recognize distinct antigens and employ immunological memory to improve the immune response upon subsequent exposures to the same antigens (Brady *et al.,*2020). The collaboration between the adaptive and innate immune systems enhances the efficacy of the adaptive immune response, resulting in the proliferation of antigen-specific T and B-cells and the generation of memory cells (Betjes, 2020).

2.15. Secretory Leukocyte Protease Inhibitor (SLPI)

Secretory Leukocyte Protease Inhibitor **(**SLPI) is a 12 kDa protein, as shown in Figure (2.5), synthesized by the cells of the human airway mucosa and is present in every fluid in the body, including saliva, tears, bronchial secretions, seminal fluid, and intestinal mucus. SLPI is recognized for its ability to block neutrophil elastase and prevent its proteolytic enzymes, which can lead to epithelium damage if left unregulated (Tarhini *et al.,*2020). Also, inhibits protease activities and reduces the transcription of proinflammatory genes via the nuclear factor-kappa B (NF-κB) pathway (Zhang *et al.,*2023).

SLPI exhibits anti-inflammatory, antibacterial and wound healing properties (Tang *et al.,*2020). SLPI preserves homeostasis in barrier tissues by inhibiting tissue degradation and modulating the intensity of inflammatory

immune responses, thereby protecting the host from infection (Nugteren & Samsom, 2021).

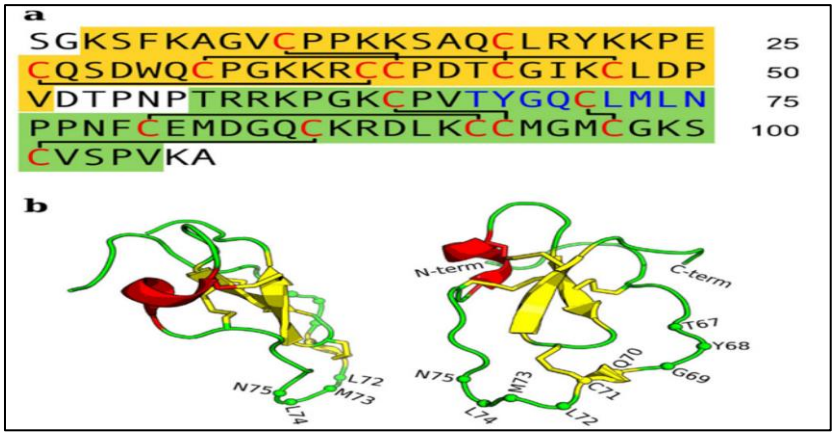


Figure (2.5): a) Amino Acid Sequence of SLPI; b) 3D Structure of SLPI (Chouyratchakarn, 2023).

2.15.1. Functions of SLPI

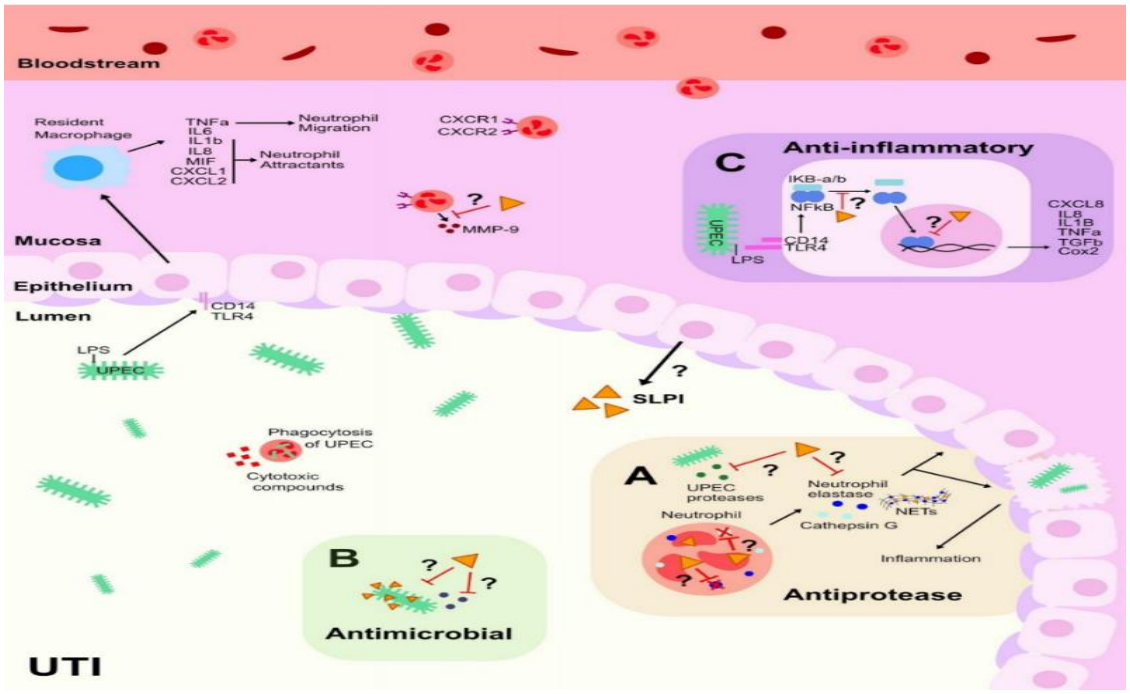
The function of SLPI can be categories by the following, as shown in Figure (2.6):

A. Antiprotease action may inhibit serine proteases released by active neutrophils, such as NE and cathepsin G. SLPI may also be observed decorated on neutrophil extracellular traps (NETs) subsequent to NETosis. Alternatively, SLPI may counteract serine proteases released by UPEC to hinder the invasion of host epithelial cells (Rosen, 2021). SLPI regulates NETosis mainly by inhibiting NE and other serine proteases, which are required for NET formation, thereby limiting chromatin decondensation and NET release. It acts as a checkpoint between antimicrobial defense and the prevention of host tissue damage (Jesus Gonzalez-Contreras *et al.,* 2025). Leukocytes release proteases to aid their movement through the extracellular matrix of tissues and to eliminate phagocytosed bacteria. Endogenous

protease inhibitors reduce the effects of these proteases to reduce peripheral tissue injury (Nugteren & Samsom, 2021).

B. SLPI has been identified as having a secondary role as an anti-inflammatory agent. It can suppress the synthesis of pro-inflammatory cytokines in cells activated by lipopolysaccharide, obstruct neutrophil infiltration in murine models of pulmonary and hepatic damage, and modulate the function of the transcription factor NF-κB (Douglas & Hannila, 2022). The regulation of inflammatory proteases, especially by endogenous anti-protease molecules, is essential for maintaining controlled and focused inflammation, ensuring that the inflammatory response is appropriately limited and restricted to the necessary degree (Mongkolpathumrat *et al.,*2024).

C. An SLPI possesses antimicrobial activity against Gram-positive, Gram-negative bacteria, mycobacteria and fungi (Munadziroh *et al.,*2020). SLPI may demonstrate bactericidal and bacteriostatic properties against invading UPEC by binding to surface molecules to prevent adhesion to the epithelium. SLPI may counteract molecular substances released by UPEC. Furthermore, SLPI may inhibit protein translation by directly binding to DNA and mRNA of bacteria (Rosen, 2021).



Figure(2.6): Proposed Mechanisms of SLPI in UTI (Rosen, 2021).

2.15.2. Role of SLPI in UTI

SLPI is primarily produced by mucosal epithelial cells and has also been identified in kidney tubular epithelial cells (Majchrzak-Gorecka *et al.,* 2016). Elevated levels of SLPI in urine have been observed in cases of cystitis, suggesting that both cytokines and SLPIs play a key role in the immune defense of the bladder mucosa and in protecting against bacterial infections during chronic UTIs (Kolesnyk *et al.,*2020). In protocol kidney biopsies, SLPI was recognized as a potential biomarker for acute kidney disease, and it was proposed that SLPI plays a role in the regeneration of renal tubular cells. The pathophysiological impacts of SLPI on renal parenchyma remain inadequately investigated (Guerrieri *et al.,*2021).

The successful invasion of hosts by bacteria is partially attributed to the emergence of advanced strategies that overcome the innate immune response.

If unresolved this may lead to the onset of systemic and serious illnesses. A prevalent strategy among various bacterial infections is the synthesis and release of proteases that destroy essential elements of the immune system (McKenna *et al.,*2022).

The findings of previous study indicated that patients with a culture positive for a uropathogen, lacking a history of rUTI exhibited higher levels of urine SLPI compared to those with a negative culture, also SLPI level was markedly elevated in pregnant women relative to non-pregnant (Rosen *et al.,* 2024). Other study conducted in mice experimentally infected with UTI and measured the levels of SLPI in urine and was markedly increased in mice infected with UTI89-Kan (Rosen, 2021).

Chapter Three

Materials and Methods

Subjects, Materials and Methods

3.1. Subjects

The present study was conducted as a case-control study at the University of Kerbala, College of Applied Medical Science, Department of Clinical Laboratories. A total of 140 individuals were enrolled in this study which classified into two equal groups. Both urine and blood samples were collected from each participant during the period from September to December 2024.

3.1.1. Groups of the Study

1. Seventy female patients with UTI were enrolled in this study whom they diagnosed by physician in Urology Consultant in Imam Hussein Medical City at Kerbala Governorate, Iraq.
2. Seventy apparently healthy female subjects were enrolled randomly. The selection was based on the absence of UTI symptoms and urine culture results.

3. Both study groups were match in age and residency in Kerbala.

3.1.2. Inclusion and Exclusion Criteria

3.1.2.1. Inclusion Criteria

1- Un-pregnant female patients with UTI.

2- Un-pregnant apparently healthy females.

3- Participants were aged between 18 and over 58 years.

3.1.2.2. Exclusion Criteria

Participants with any of the following conditions were excluded from the current study:

1- COVID-19

2- Asthma

3- Cardiovascular disease

4- Cancer

5- Diabetes mellitus

6- Autoimmune disease

7- Chronic kidney disease

8- Urinary tract anatomic abnormalities (including nephrolithiasis)

9- Pregnancy

3.1.3. Questionnaire

Information from each participant within each group was documented like, age, educational state (student, an employee), marital status (single or married), possibility of pregnancy, use of a urinary catheter, history of recurrent UTI, symptoms of UTI (burning, urgency, frequency of urination and back pain), using any antibiotics, time of menstrual period, the menarche status (reproductive period or postmenopausal), urination status (continence- incontinence), weights, heights, presence of hypertension, information about smoking and some hygienic practice as shown in the Appendix (1).

3.1.4. Ethical Consideration

This study was approved by the Ethical Committee at the College of Applied Medical Science/ University of Kerbala (Ref.: CLAMSKU/8) and the Ethical Committee at Imam Hussein Medical City at Kerbala. Before collecting the sample, all individuals included in the current study were informed and agreed to participate in this work verbally.

3.1.5. Study Design

A Case-control study design was conducted, as shown in Figure (3.1).

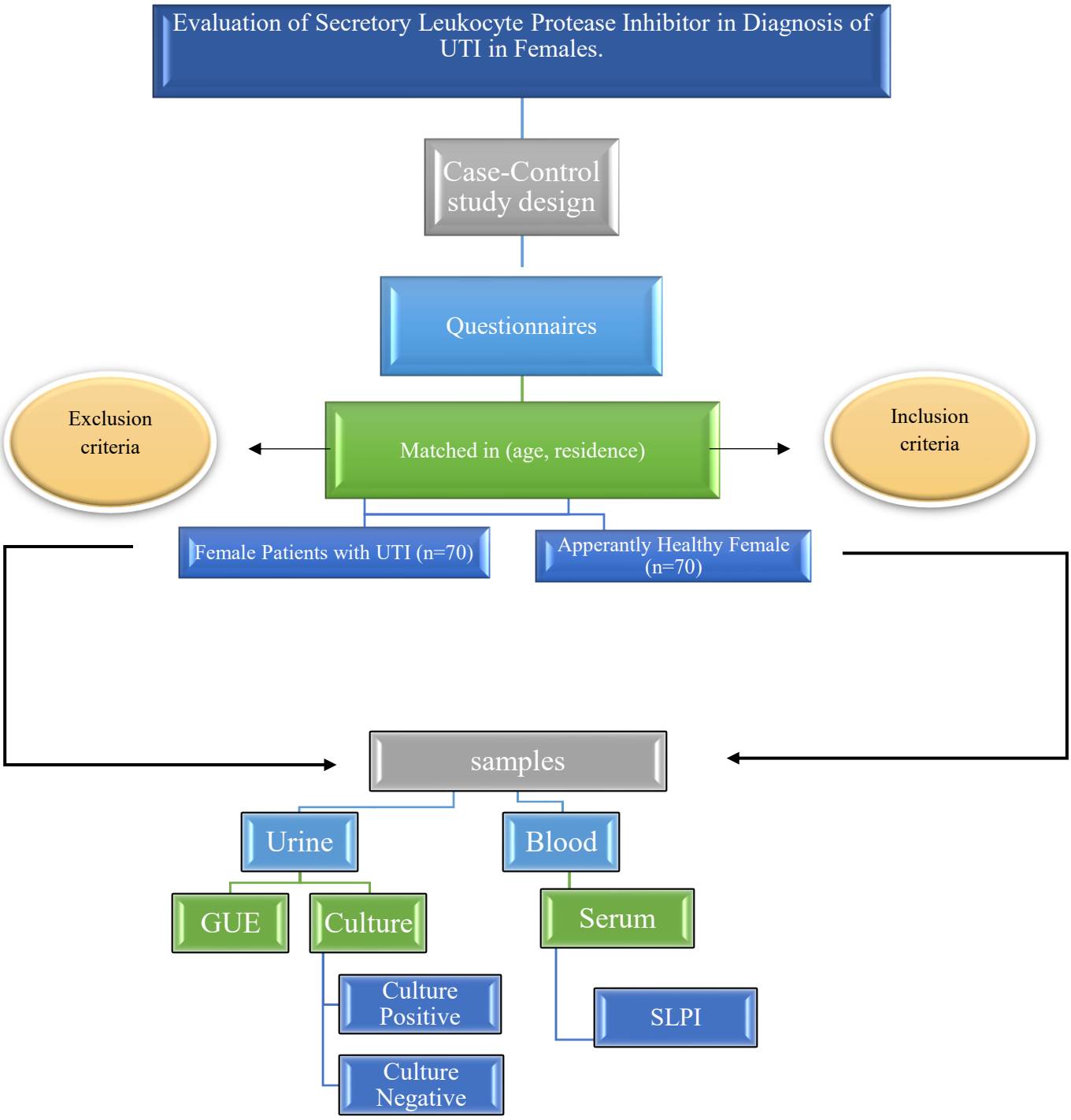


Figure (3.1): Study Design

3.2.Materials

3.2.1. Kits and Chemical Materials

Table (3.1) shows the chemicals and kits that were used in this study.

Table (3.1): Kits and Chemicals.

No	Chemicals and Kits	Company	Country
1.	Blood agar media	HIMEDIA	India
2.	Dipstick	Cybow	Korea
3.	MacConkey agar media	HIMEDIA	India
4.	SLPI ELISA kit	BT LAB	China
5.	VITEK kit	Marcy l'Etoile	France

3.2.2. Tools

The following tools were used in the current study, as shown in Table (3.2).

Table (3.2): Tools of Current Study.

No	Tools	Company	Country
1.	Alcohol	Aljoud	Iraq
2.	Beaker, Conical flask, Glass wear, Cylinder	AFCO	Jorden
3.	Disposable loops, Disposable pipette, Sticks	CITOTEST	China
4.	Disposal Syringes 3 ml	AL-Shaghaf	China
5.	Eppendorf tube, Gel tube, Slides	TRUST LAB	China
6.	Gloves	KINGFA/MEDICAL	China
7.	Mask, Petri dishes, Pipette Tips, Plane tube, Cotton	TKMD	Germany
8.	Tourniquet	Voltaren	China
9.	Urine container	xinkkang	China

3.2.3. Apparatuses and Equipment

The instruments and apparatuses that utilized in this study was show in Table (3.3).

Table (3.3): The Equipment and Apparatuses.

No	Apparatus and Equipment	Company	Country
1.	Autoclave	Hirayama	Japan
2.	Biological Cabinet	Con – test	Canada
3.	Centrifuge	Kukusan	Japan
4.	ELISA printer, ELISA reader, ELISA washer	PARA Medical	Italy
5.	Incubator, Water bath	Memmert	Germany
6.	Magnetic stirrer, Water Distilling, Benson Burner	GEL	Germany
7.	Microscope	Olympus	Japan
8.	Oven	Hanshin	Korea
9.	Refrigerator	HITACHI	Japan
10.	Sensitive balance	Tafesa	Germany
11.	VITEK 2 Compact	Biomerieux	France
12.	Vortex	Scientific Industries	Korea

3.3. Methods

3.3.1. Collection Samples

The blood and urine samples were collected from both female patients following diagnosis by urologist and apparently healthy female.

3.3.1.1. Collection of The Blood Sample

Three milliliters of venous blood were drawn from all participant by using a disposable syringe. The collected blood was put into a gel tube and allowed to set at room temperature for 20 minutes. For serum collection, the gel tube centrifuged at 5000 round per minute (rpm) for 10 minutes and then the serum was put into Eppendorf tubes and stored at (-20˚C) until using it to estimate the secretory leukocyte protease inhibitor (SLPI) (Schnell *et al.,* 2002).

3.3.1.2. Collection of The Urine Samples

A disposable sterile plastic container was used. About 5 ml "midstream" of urine was collected from each female sample and were centrifuged. Centrifuged samples were used for GUE and culture on standard culture media, including MacConkey and blood agar. The samples were then incubated under aerobic conditions at (37 °C) for a period of 24-48 hours (Llor *et al.,* 2023)**.**

3.3.2. Determination The Body Mass Index (BMI)

BMI is not a direct measure of body fat and it is a widely used diagnostic tool for identifying underweight, normal weight, overweight, obese, or morbidly obese individuals (Messiah, 2020). BMI can be calculated using metric or imperial (US) units. Metric units: weight (kilograms) divided by height squared (meters): BMI = kg/m^2 (Zierle-Ghosh & Jan, 2018).

3.3.3. Dipstick Test

It is the quickest way to test urine; a specially treated paper strip was dipped into centrifuged samples. The results are usually available within 60 to 120 seconds. The strip has squares on it that change color in the presence of certain substances. Next, the strip result will be compared to a chart located on the side of the urine testing strip package. Often the more intense the color change, the more of the substance there is in the urine.

3.3.4. General Urine Examination (GUE)

Upon receiving the urine sample, 5 mL was centrifuged at 1700 g-force for 5 minutes. The supernatant was removed and the sediment was resuspended and by examined at low power (10 × objective) and high power (40 × objective) using light microscope (Palsson *et al.,* 2020). Slides were air-dried, mounted, and analyzed for the presence of crystals, casts, leukocytes, erythrocytes, or bacterial/yeast infections.

3.3.5. Preparation of Culture Media

3.3.5.1. Blood Agar

Forty grams of blood agar base powder were dissolved in 1000 mL of distilled water. The mixture was autoclaved at 121°C for 15 minutes to achieve sterilization. Following cooling, 5-7% of sterile defibrinated blood was added and then the media was poured into the petri plates (Niederstebruch *et al.,* 2017).

3.3.5.2. MacConkey Agar (MCA)

It is a selective and differential medium utilized for isolation and distinguishing rapidly proliferating Gram-negative bacteria, particularly those belonging to the *Enterobacteriaceae* family (Supriatin *et al.,* 2021). Suspend 49.53 grams of agar dissolved in 1000 mL of distilled water. The media was sterilized for 15 minutes at 121°C in an autoclave, then cooled to 40-50°C before being poured into petri dishes. Plates were stored in the refrigerator until it is used (Bozaslan *et al.,* 2016).

3.3.6. Isolation of Bacteria

A loopful of sample was inoculated onto MacConkey agar (MCA) and blood agar. The inoculated plates were then incubated aerobically at 37°C for 24 hours. Bacterial classification based on Gram reaction was performed using the Gram staining technique. This process involved transferring a small portion of a bacterial colony onto a clean glass slide using a drop of normal saline and spreading it evenly. The bacterial suspension was placed on the glass slide and fixed by gentle heating. The smear was first stained with crystal violet, followed by the application of iodine, which forms a complex with the primary dye. Decolorization was carried out using alcohol or acetone to differentiate bacteria based on cell wall structure and thickness. Finally, safranin was applied to the specimen for 1 minute as a counterstain. The

stained bacteria were examined under a light microscope to determine their Gram reaction (Paray *et al.,* 2023).

3.3.7. Identification of Bacteria

The bacterial identification was done through the use of automated devise. The VITEK2 system has become the backbone of diagnostic microbiology labs even in developing countries (Khurana *et al.,* 2020). The integrated VITEK 2 system is a closed system comprises the filler-sealer unit, reader-incubator, computer control module, data terminal, and multi-copy printer. This devise facilitates the identification of chemical reactions and bacterial proliferation within the microwells of thin plastic cards (El-Amier *et al.,* 2024). It employs 64-well cards including a barcode that encodes the card type, expiration date, lot number, and unique identification number. Available test kits comprise ID-GN (identification of Gram-negative) and ID-GP (identifying of Gram-positive) (Duraye *et al.,* 2024).

3.3.8. Determination of Secretory Leukocyte Protease Inhibitor (SLPI)

3.3.8.1. Assay Principle

This kit was an Enzyme-Linked Immunosorbent Assay (ELISA). The plate had been pre-coated with human SLPI antibody. SLPI present in the sample was added and bound to antibodies coated on the wells. Then, biotinylated human SLPI antibody was added and bound to SLPI in the sample. Then, streptavidin-HRP was added and bound to the biotinylated SLPI antibody. After incubation unbound streptavidin-HRP was washed away during a washing step. Substrate solution was then added and color develops in proportion to the amount of human SLPI. The reaction was terminated by addition of acidic stop solution and absorbance was measured at 450 nm.

3.3.8.2. Kit Component

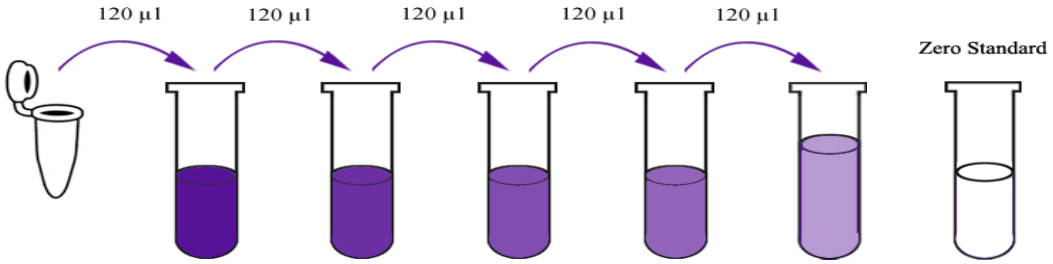
Table (3.4): SLPI ELISA Kit Components.

No	Components	Quantity (96T)	Quantity (48T)
1.	Biotinylated Human SLPI Antibody	1ml x1	1ml x1
2.	Plate Sealer	2 pics	2 pics
3.	Pre-coated ELISA Plate	12 * 8 well strips x1	12 * 4 well strips x1
4.	Standard Diluent	3ml x1	3ml x1
5.	Standard Solution (4800ng/L)	0.5ml x1	0.5ml x1
6.	Stop Solution	6ml x1	3ml x1
7.	Streptavidin-HRP	6ml x1	3ml x1
8.	Substrate Solution A	6ml x1	3ml x1
9.	Substrate Solution B	6ml x1	3ml x1
10.	User Instruction	1	1
11.	Wash Buffer Concentrate (25x)	20ml x1	20ml x1
12.	Zipper bag	1 pic	1 pic

3.3.8.3. Assay Procedure

- All reagents, standard solutions, and samples were prepared as instructed. All reagents were brought to room temperature before use. The assay was performed at room temperature.
- The number of strips required for the assay was determined. The strips were inserted into the frames for use. The unused strips were stored at 2-8°C.
- Fifty µl of standard was added to the standard well. Biotinylated antibody was not added to the standard well because the standard solution contained biotinylated antibody.
- Forty µl of sample was added to the sample wells, followed by 10µl of anti-SLPI antibody. Then, 50µl of streptavidin-HRP was added to the sample wells and standard wells (not the blank control well). The contents were mixed well. The plate was covered with a sealer and incubated for 60 minutes at 37°C.

- The sealer was removed, and the plate was washed 5 times with wash buffer automatically. Each well was soaked with 300µl of wash buffer for 30 seconds to 1 minute for each wash. Each well was aspirated or decanted and washed 5 times with wash buffer. The plate was blotted onto paper towels or other absorbent material.
- Fifty µl of substrate solution A was added to each well, followed by 50µl of substrate solution B. The plate was incubated for 10 minutes at 37°C in the dark, covered with a new sealer.
- Fifty µl of stop solution was added to each well, causing the blue color to change to yellow immediately.
- The optical density (OD value) of each well was determined immediately using a microplate reader set to 450 nm within 10 minutes after adding the stop solution.



3.3.8.4. Calculation of Result

A standard curve was constructed by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis and a best fit curve was drawn through the points on the graph. These calculations can be best performed with computer-based curve-fitting software and the best fit line can be determined by regression analysis.

Fit the non-linear regression equation= A [i] * x + B [i], correlation coefficient =0.990.

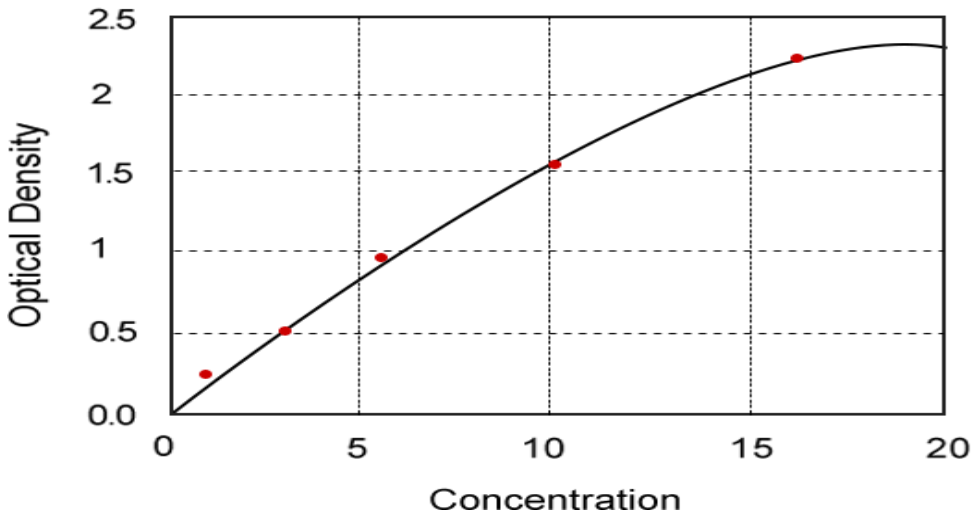


Figure (3.2): Standard Curve for SLPI.

3.3.9. Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), version 25 software (IBM Corp., NY, and USA), was used to analyze data. Descriptive statistics were used to determine frequencies, the mean with standard deviation, standard error, and cross-tabulation. Numerical data was tested for normality. If the variable followed the normal distribution, then the parametric test was used. If the variable does not follow the normal distribution, non-parametric test was used. Categorical variables were tested using chi-square test. The statistical significance level was established at $P \leq 0.05$. To determine whether any significant positive and negative correlations were present between variables, the Bivariate correlations was analyzed. Receiver Operating Characteristics (ROC) curve analysis was used to determine the discriminatory ability of some variables (Rahman & Muktadir, 2021).

Chapter Four
Results and Discussion

4.1. Demographic Data of UTI Patients and Apparently Healthy Control.

The current study involves 70 Female patients with UTI and 70 health females whom they screened for the presence of ABU. Based on the presence of significant bacterial growth in urine culture, the two groups were classified into two subgroups, as shown in Table (4.1). Forty patients (57.1%) had bacterial growth and 30 (42.9%) had no bacterial growth. On the other hand, 28 (40.0%) of healthy subjects had bacterial growth which were considered as ABU and the rest were without growth.

Table (4.1) Demographic Data of UTI Patients and Apparently Healthy Control.

Variable	UTI Patients		Total Number	Apparently Healthy Control		Total Number	P-Value
	With bacterial growth	Without bacterial growth		With bacterial growth	Without bacterial growth		
N (%)	40(57.1)	30(42.9)	70(100.0)	28(40.0)	42(60.0)	70(100.0)	
Age (Mean ±SD)	39.36±14.28		70	39.10±14.38		70	NS
Age groups in Years			**N (%)**				
18 - 37	22(61.1)	14(38.9)	36(51.4)	16(47.1)	18(52.9)	34(48.6)	NS
38 - 57	14(53.8)	12(46.2)	26(37.1)	7(25.9)	20(74.1)	27(38.6)	
≥ 58	4(50.0)	4(50.0)	8(11.4)	5(55.6)	4(44.4)	9(12.9)	
Marital Status			**N (%)**				
Single	5(45.5)	6(54.5)	11(15.7)	7(41.2)	10(58.8)	17(24.3)	NS
Married	35(59.3)	24(40.7)	59(84.3)	19(38.0)	31(62.0)	50(71.4)	
Divorced	0(0.0)	0(0.0)	0(0.0)	2(66.7)	1(33.3)	3(4.9)	
Educational state			**N (%)**				
Student	5(71.4)	2(28.6)	7(10.0)	4(44.4)	5(55.6)	9(12.9)	NS
Employee	3(50.0)	3(50.0)	6(8.6)	4(25.0)	12(75.0)	16(22.9)	
Housewife	32(56.1)	25(43.9)	57(81.4)	20(44.4)	25(55.6)	45(64.3)	
Menarche status			**N (%)**				
Reproductive	29(58.0)	21(42.0)	50(71.4)	25(43.1)	33(56.9)	58(82.9)	NS
Menopause	11(55.0)	9(45.0)	20(28.6)	3(25.0)	9(75.0)	12(17.1)	
Smoking			**N (%)**				
Yes	2(100.0)	0(0.0)	2(2.9)	2(100.0)	0(0.0)	2(2.9)	NS
No	38(55.9)	30(44.1)	68(97.1)	26(38.2)	42(61.8)	68(97.1)	
BMI(Mean±SD)	26.99±0.75[a]	30.09±0.89	70	30.40±1.34	28.57±0.87	70	0.048*
BMI Groups (kg/m2)			**N (%)**				
Normal < 25	16(66.7)	8(33.3)	24(34.3)	4(26.7)	11(73.3)	15(21.4)	NS
Overweight 25-29	13(65.0)	7(35.0)	20(28.6)	11(44.0)	14(56.0)	25(35.7)	
Obese ≥ 30	11(42.3)	15(57.7)	26(37.1)	13(43.3)	17(56.7)	30(42.9)	

N, Number; SD, Standard Deviation; *, Significant at 0.05 level between UTI and Healthy Group; NS, Not Significant at 0.05 level; UTI, Urinary Tract Infection; BMI, Body Mass Index; [a], Values Differ Significantly at 0.05 Level within UTI and Healthy Subgroups.

UTI is the colonization of the urinary tract by uropathogenic bacteria, resulting in varying degrees of inflammatory reaction (Hernández-Hernández *et al.,* 2022). Bacterial growth is highly common in UTIs, as numerous studies emphasize the important role of certain pathogens and their patterns of antibiotic resistance (Ali *et al.,* 2024). Similar findings were documented, in previous study in which, (65.5%) of female suffering from UTI were tested positive for bacterial isolates and (34.55%) were culture-negative (Sharma *et al.,* 2020). In a study by Biggel *et al.,* (2019) reported a (45.7%) prevalence of ABU among females.

One of the reasons for negative urine culture is that a considerable number of patients presenting with UTI symptoms may actually have sexually transmitted infections, such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, which can result in negative urine cultures due to the lack of common uropathogens. Also, prior antibiotic treatment can inhibit bacterial growth in urine cultures, leading to negative results even when UTI symptoms are present (Olaru *et al.,* 2021). Furthermore, standard urine culture has significant limitations, these limitations include the inability to identify slow-growing microorganisms, the failure to cultivate fastidious and non-aerobic microorganisms, and the incapacity to detect microorganisms present in concentrations below 10^3 CFU/mL (Price *et al.,* 2018).

The mean age of both groups was (39.36±14.28) and (39.10±14.38), respectively. The higher frequency of UTI patients and healthy groups were in the age category 18-37 years. The age and residency were matched between the two groups. Thus, no significant differences were noticed among all age groups, as shown in Table (4.1). Similar result was found in previous study (Johny *et al.,* 2025). It had been documented that the highest incidence of UTIs occurred during the years of peak sexual activity, typically between the ages of 18 and 39 (Medina & Castillo-Pino, 2019b). A statistically significant association between adults age and the occurrence of UTIs was demonstrated by Hantoosh *et al.,* (2016).

Thirty-five (59.3%) of UTI patients were married and had bacterial growth. This result was similar to the findings of Saber *et al.* (2021), who reported that the majority of UTI cases (61.2%) occurred in married females. Fifty-seven (81.4%) from total UTI patients and 45 (64.3%) of healthy subjects were housewives, (56.1%) and (44.4%) of them had bacterial growth, respectively. The occurrence of UTIs among married individuals was influenced by a combination of anatomical, behavioral, and social factors. Studies suggested that married women, in particular, experienced a higher rate of UTIs, often associated with urinary incontinence and sexual activity. Both of which could facilitate the entry of pathogens into the urinary tract during intercourse (Subramaniam *et al.,* 2016).

Regarding the menarche status, 50 (71.4%) and 58 (82.9%) of both UTI and healthy groups were in the reproductive state, (58.0%) and (43.1%) of them had bacterial growth, separately. The prevalence of UTIs in women of reproductive age is growing daily. The main factors leading to the prevalence of UTIs include unsanitary menstrual practices and sexual intercourse (Johny *et al.,* 2025). Previous study recorded the prevalence of UTIs among females of reproductive age was (65.0%) (Saber *et al.,* 2021). Saxena *et al.,* (2023) reported a lower prevalence rate of bacterial growth among females in the reproductive stage. The differences in the prevalence between the current study and the mentioned study is due to their small sample size (105 samples).

Regarding smoking status, approximately all of the participant in both groups were nonsmoker. The total number of female smokers is far lower than that of male smokers, due to the fact that phenomenon of women smoking is shaped by social and cultural values (Rosemary, 2025). A study conducted in Erbil city/Iraq on the prevalence of smokers found that most female participants were non-smoker. This result may be attributed to the community disapproval, which discourages female from smoking (Younus *et al.,* 2023).

Concerning BMI, the current study revealed that the mean ± of BMI in UTI patients' subgroups was (26.99±0.75 and 30.09±0.89) and in healthy participant subgroups were (30.40± 1.34 and 28.57± 0.87), as shown in table (4.1). The higher frequency of participants was in obese category. It has been documented that obesity is associated with an increased risk of having UTI in both males and females. Individuals with obesity had a 2.5-times increased probability of being diagnosed with UTI compared to their non-obese (Kim *et al.,* 2021). The results of a previous study showed the occurrence of UTI attributable to BMI, grouped by specific sex and age categories.

4.2. Behavioral Practice Between UTI Patients and Apparently Healthy Controls.

Various hygiene-related variables were assessed between the two study groups to understand if there were any association between these behaviors and disease, as shown in the table (4.2). The analysis revealed that there were negative association between disease occurrence and hand wash, hygienic product, and wear cotton undergarment. Whereas there were positive association between disease occurrence and washing underwear by hand and bath frequency (higher frequencies were seen in UTI patients). No association was found regarding usage of toilet paper. Perineal hygiene and toilet habits play a crucial role in the transmission and spread of UTIs, especially in females. Wiping vaginal area from back to front during urination enhancing the bacteria transfer from the anal region to the urethra and increasing the risk of UTIs (Tindimwebwa, 2023). Proper practice of perineal hygiene following urination and during menstruation might reduce the risk of UTIs as well as diseases associated with the genital area. The frequency of changing underwear is seen as an essential aspect of hygiene practices, as the prolonged use of moist cloth promotes bacterial proliferation and heightens the risk of infection (Jelly *et al.,* 2022). The Mohanty *et al.,* (2018) suggests that personal hygiene habits, such as washing

underwear, can impact the risk of UTIs and women typically establish their hygiene routines based on cultural influences and educational background.

Table (4.2) Behavioral Practice between UTI Patients and Apparently Healthy Control.

Variable	UTI Patients N (%)	Apparently Healthy Control N (%)	Total Number N (%)	P-Value	Odds Ratio For cohort = Patients	CI 95% (Lower-Upper Limits)
Hand Wash						
Yes	47(42.7)	63(57.3)	110(100.0)	0.002*	0.55	0.56 (0.42-0.75)
No	23(76.7)	7(23.3)	30(100.0)			
Using Toilet Paper						
Yes	16(50.0)	16(50.0)	32(100.0)	1.000	1	1.00 (0.67-1.48)
No	54(50.0)	54(50.0)	108(100.0)			
Using Hygienic Products						
Yes	23(39.7)	35(60.3)	58(100.0)	0.59	0.69	0.69 (0.48-1.00)
No	47(57.3)	35(42.7)	82(100.0)			
Wear Cotton Undergarment						
Yes	45(45.9)	53(54.1)	98(100.0)	0.196	0.77	0.77 (0.56-1.07)
No	25(59.5)	17(40.5)	42(100.0)			
Washing Undergarment						
By Hand	41(51.9)	38(48.1)	79(100.0)	0.733	1.092	1.09 (0.78-1.53)
With Machine	29(47.5)	32(52.5)	61(100.0)			
Bath Frequency						
Every day	34(66.7)	17(33.3)	51(100.0)	0.005*	1.64	1.65 (1.19-2.27)
≥ Two/ Week	36(40.4)	53(59.6)	89(100.0)			
N, Number; UTI, Urinary Tract Infection; *, Significant at 0.05 level between UTI and Healthy Group.						

4.3. Clinical Data of UTI Patients and Controls.

This study investigated the presence of recurrent UTI, prior antibiotic use, and different urinary symptoms among the two studied groups, as shown in Table (4.3). The two study groups were subdivided in two subgroups in order to study the presence and frequency of the investigated parameters within subgroups. About 59 (84.3%) of UTI patients had rUTI, among them, 32 (54.2%) had significant bacterial growth. While, 11(15.7%) of UTI patients had no history of rUTI, among them 8 (72.7%) with bacterial growth. On the other hand, 26 (37.1%) of healthy control had rUTI, among them, 10 (38.5%) had positive bacterial growth. There was significant difference patient and healthy control.

Table (4.3) Clinical Data of UTI Patients and Apparently Healthy Controls.

Variable	UTI Patients		Total Number	Apparently Healthy Controls		Total Number	Chi-Square
	With bacterial growth	Without bacterial growth		With bacterial growth	Without bacterial growth		
N (%)	40(57.1)	30(42.9)	70(100.0)	28(40.0)	42(60.0)	70(100.0)	
Recurrent UTI							
With rUTI	32(54.2)	27(45.8)	59(84.3)	10(38.5) [a]	16(61.5)	26(37.1)	0.000*
Without rUTI	8(72.7)	3(27.3) [a]	11(15.7)	18(40.9)	26(59.1)	44(62.9)	
P-Value	0.331			1.000			
Symptoms: -							
1-Burning							
Present	32(52.5)	29(47.5)	61(87.1)	0(0.0)	0(0.0)	0(0.0)	NS
Absent	8(88.9)	1(11.1)	9(12.8)	28(40.0)	42(60.0)	70(100.0)	
P-Value	0.068			-------			
2-Urgency							
Present	32(58.2)	23(41.8)	55(78.6)	0(0.0)	0(0.0)	0(0.0)	NS
Absent	8(53.3)	7(46.7)	15(21.4)	28(40.0)	42(60.0)	70(100.0)	
P-Value	0.775			-------			
3-Frequency of Urination							
Present	25(49.0)	26(51.0)	51(72.9)	0(0.0)	0(0.0)	0(0.0)	0.031*
Absent	15(78.9)	4(21.1) [a]	19(27.1)	28(40.0)	42(60.0)	70(100.0)	
P-Value	0.031*			-------			
4-Suprapubic Pain							
Present	33(62.3)	20(37.7)	53(75.7)	0(0.0)	0(0.0)	0(0.0)	NS
Absent	7(41.2)	10(58.8)	17(24.3)	28(40.0)	42(60.0)	70(100.0)	
P-Value	0.163			-------			
Urination							
Continence	17(63.0)	10(37.0)	27(38.6)	19(35.2)	35(64.8)	54(77.1)	NS
Incontinence	23(53.5)	20(46.5)	43(61.4)	9(56.3)	7(43.8)	16(22.9)	
P-Value	0.468			1.55			
Hypertension							
Yes	9(64.3)	5(35.7)	14(20.0)	6(40.0)	9(60.0)	15(21.4)	NS
No	31(55.4)	25(44.6)	56(80.0)	22(40.0)	33(60.0)	55(78.6)	
P-Value	0.764			1.000			
Using Antibiotics							
Yes	13(59.1)	9(40.9)	22(31.4)	7(41.2)	10(58.8)	17(24.3)	NS
No	27(56.3)	21(43.8)	48(68.6)	21(39.6)	32(60.4)	53(75.7)	
P-Value	1.000			1.000			

N, Number; NS, Not Significant; *, Significance at 0.05 level between UTI and Healthy Group; UTI, Urinary Tract Infection; [a], Values Differ Significantly at 0.05 Level within UTI and Healthy Subgroups.

Similarly, Al-Musawi & Al-Husseini, (2021) documented that more than three-quarters of the patients (82.4) experience rUTIs. The rUTI are typically defined as culture-confirmed UTIs that occur at least twice within six months or three times within a year (Aslam *et al.,* 2020). The resident microbial population in the urinary

system, or urine microbiome, likely contributes to both sporadic and rUTIs (Hernández-Hernández *et al.,* 2022a). One reason that could potentially influence the risk of UTI recurrence is that the choice of empirical therapy used to treat UTIs may not be well characterized. Additionally, UTIs are frequently treated inappropriately (Hamilton & Fishman, 2014).

Regarding burning sensation, 61 (87.1%) of UTI patients had this symptom, among them 32 (52.5%) had significant bacterial growth. Whereas, none of the healthy control group had it. In a similar study, nearly three-quarters of patients, or (84.6%) had pain during urination (Alshahrani *et al.,* 2022). UTIs are typically characterized by burning sensation while urinating, which may occur with or without urinary frequency, and suprapubic discomfort. It is important to recognize that these symptoms do not definitively indicate that the individual has UTIs (Kaur & Kaur, 2021).

Fifty-five (78.6%) of UTI patients had urgency, among them 32 (58.2%) with bacterial growth. Fifty-one (72.9%) of UTI patients had frequency of urination and 25 (49.0%) of them had bacterial growth, there were significant difference among the four subgroups. Urgency refers to the intense need to urinate, resulting from the voluntary contraction of the bladder muscles (Iscoe *et al.,* 2024). Frequent urination and a strong urge to urinate are commonly experienced, often accompanied by discomfort in the lower abdomen (Yang & Foley, 2020). de Freitas & Faria, (2020) reported a frequency of urination was (75.5%) and a higher frequency of urgency (91.8%), this variation may be due to differences in the sample size between the two studies.

About 53 (75.7%) and 27 (38.6%) of UTI patients had suprapubic pain and continence among them 33 (62.3%) and 17 (63.0%) had bacterial growth. From the symptoms of UTIs are discomfort in lower abdomen region, even when passing little amount of urine (Kaur & Kaur, 2021). Suprapubic pain was the more prevalent

symptom observed in UTI patients, occurring in (73.3%) cases, as reported in a previous study (Sanilkumar *et al.,* 2023). Urinary incontinence is defined as the involuntary leakage of urine (Denisenko *et al.,* 2021). Elevated incidences of incontinence were observed in females compared to males, particularly in those with a rising frequency of UTIs (Elliott *et al.,* 2025).

It has been documented that neurogenic bladder dysfunction directly affects bladder filling and emptying, leading to urinary infection and incontinence (Storme *et al.,* 2019). Also, the rUTIs have a profound effect on bladder physiology, causing persistent dysfunction and pain. Studies suggested that rUTIs trigger neurogenic changes, inflammatory reactions, and structural modifications in the bladder, which can persist symptoms even after the infection has been cleared (Hayes *et al.,* 2024). Furthermore, the examination of the bladder's umbrella cells and tight junctions reveals defects in patients with rUTIs, leading to impaired bladder function (Jhang *et al.,* 2022). This is proved by this study in which most of patients whom they have incontinence had history of rUTI.

There were no significant differences among the four subgroups regarding hypertension and history for prior use of antibiotics. Hypertension and UTIs are interconnected health concerns that have great effect on patients outcomes (Marlina *et al.,* 2025). This indicates that although hypertension may be associated with UTIs, the drugs used to treat it do not increase the probability of developing UTIs (Gremke *et al.,* 2023). Unnecessary use of antibiotics can lead to antimicrobial resistance and disturb the natural balance of microbiota in the urinary tract. The choice of antibiotics and the length of treatment depend on several factors, such as the infection's location, the severity of symptoms, and characteristics of both the bacterial pathogen and the host (Baimakhanova *et al.,* 2025). Although the existence of these findings, some studies suggest the importance of antibiotic stewardship,

noting that inappropriate prescribing may lead to complications such as antibiotic resistance (Khan *et al.,* 2023).

4.4. Comparison of SLPI According to Demographic Data of UTI Patients and Apparently Healthy Control

To the best of the researcher's knowledge, this is the first study that evaluates the importance of serum SLPI level in patients with UTI as diagnostic biomarker and the possible usage of this protein. This study found that there was no significance difference in the mean of serum level of SLPI between patients and control group. Besides, it has been documented that SLPI levels are known to rise in response to UTIs, as demonstrated in both human and mouse studies. However, In humans, increased SLPI concentrations in the blood and urine are linked to pyelonephritis, suggesting its involvement in the development and worsening of chronic pyelonephritis (Kolesnyk *et al.,* 2020). Non-significant difference in the serum level of SLPI in the current study could be attributed to the fact that this study did not include patients with pyelonephritis.

Comparative analysis of SLPI serum level based on different demographic variables revealed that there were significant differences in the mean level of SLPI between the two groups according to age category (18-37) years and overweight (higher mean level was seen in control group).

Comparison the level of SLPI within each group according to the demographic variables revealed significant differences in age categories of healthy group (higher level was seen in younger age), menarche status (higher level in reproductive state), marital status (higher level was seen in single state), and educational status (higher level in employee females) and in BMI categories and marital status in UTI patients, as offered in Table (4.4).

Table (4.4) Comparison of SLPI According to Demographic Data of UTI Patients and Apparently Healthy Control.

Variables	UTI Patients			Apparently Healthy Controls			Mann Whitney Test / P- Value
	N	Mean Rank	Mean ± SE	N	Mean Rank	Mean ± SE	
SLPI	70	67.57	390.58±52.14	70	73.43	390.35± 40.18	0.39
Kruskal Wallis Test/ P- Value	NS						----------
Age Categories:							
18-37	36	36.31	434.15±95.12	34	42.88	491.48±77.95	0.03*
38-57	26	37.15	365.79±46.71	27	32.07	313.47±17.91	0.72
≥58	8	26.50	275.10±46.58	9	17.89	238.92±23.94	0.63
Kruskal Wallis Test/ P- Value	NS			0.003*			---------
BMI Categories:							
Normal Weight	24	46.21	580.10±142.63	15	44.87	615.29±167.60	0.79
Over Weight	20	24.65	275.62±30.84	25	33.20	328.77±21.02	0.02*
Obese	26	33.96	304.08±18.39	30	32.73	329.20±27.70	0.73
Kruskal Wallis Test/ P- Value	0.002*			NS			---------
Menarche status:							
Reproductive	50	37.26	410.26±69.37	58	39.81	424.19±47.19	0.11
Menopause	20	31.10	341.40±57.92	12	14.67	226.79±19.07	0.15
Kruskal Wallis Test/ P- Value	NS			0.000*			---------
Marital Status							
Single	11	46.64	757.55±295.68	17	51.35	644.77±146.35	0.49
Married	59	33.42	322.17±22.67	50	29.62	304.59±13.94	0.87
Divorced	0	---------	---------	3	43.67	378.00±67.22	---------
Kruskal Wallis Test/ P- Value	0.048*			0.001			---------
Educational State							
Student	7	43.14	425.08±100.06	9	43.67	415.13±57.22	0.71
Employee	6	43.83	924.87±533.53	16	49.94	638.49±155.79	0.71
Housewife	57	33.68	330.11±26.51	45	28.73	297.16±13.41	0.65
Kruskal Wallis Test/ P- Value	NS			0.001*			---------
Smoking							
Yes	2	21.50	251.20±35.48	2	34.50	333.34±5.19	0.21
No	68	35.91	394.68±53.60	68	35.53	392.03±41.35	0.48
Kruskal Wallis Test/ P- Value	NS			NS			---------

N, Number; *, Significant at 0.05 level between UTI and Healthy Group; NS, Not Significant at 0.05 level; SLPI, Secretory Leukocyte Protease Inhibitor; SE, Standard Error; BMI, Body Mass Index.

A study conducted by Kolesnyk *et al.,* (2020) showed that the serum SLPI level in children was higher than in adults. However, in another study aimed to

measure oral SLPI level in oropharyngeal cancer, they found that there was no statistically significant difference in SLPI levels according to age categories within both the patient and control groups (Dickey *et al.,* 2021). In another study, salivary SLPI concentrations were significantly lower in elderly individuals compared to younger adults (Rahman *et al.,* 2016). This decline in SLPI may impair mucosal defenses, increasing the risk of infections in older adults. This might be because the physiological decline in older population affects all body systems, decreasing the body's capacity to maintain homeostasis when the body confronted with a stressor (Preston & Biddell, 2021).

A study of more than 4,600 participants identified 152 proteins linked to BMI, highlighting a complex relationship between obesity and serum protein patterns, especially those involved in lipid metabolism and inflammation (Zaghlool *et al.,* 2020). SLPI plays a crucial role in regulating the immune response, especially in inflammatory conditions. It helps protection tissues from damage by inhibiting proteolytic enzymes that are released during inflammation (Douglas & Hannila, 2022). Dietary habits affect protein levels; the higher protein intake being associated with elevated plasma protein levels. Women who maintain a higher-quality diet tend to exhibit improved health indicators (Tore *et al.,* 2023). The use of dietary supplements, including protein products, can contribute to increased overall protein levels in the body (Witkoś & Hartman-Petrycka, 2022). Obesity is a chronic inflammatory condition that may be associated with decreased level of serum SLPI (Hochberg *et al.,* 2021).

Throughout their reproductive years, women undergo monthly hormonal changes as part of the menstrual cycle. These fluctuations influence the entire body, including the immune system (Zwahlen & Stute, 2024). Changes in hormone levels can influence SLPI expression, potentially impacting the inflammatory response during UTIs (Sanyaolu *et al.,* 2023). Epithelial cells in the female genital tract

produce antimicrobial peptides such as SLPI. It has been documented that in the endometrium, SLPI levels vary throughout the menstrual cycle, reaching their peak during the reproductive phase (Lessey & Young, 2019).

The connection between daily work stress and inflammation differed based on marital status and relationship quality. In particular, unmarried individuals exhibited a stronger stress-inflammation link. This highlights the protective effect of strong marital relationships against stress-related inflammation (Park *et al.,* 2024). Both sex may be impacted differently by regional variations in material living standards and work situations (Pedrós Barnils *et al.,* 2020). The psychological effects of motherhood on women's mental health and overall well-being are complex, frequently presenting considerable problems. Studies show that mothers may experience a gradual decline in mental well-being, especially in contrast to women without children, who generally exhibit more consistent mental health (Kuipers *et al.*, 2021).

4.5. Comparison Between SLPI and Clinical Data of UTI Patients.

Comparison the SLPI mean level according to clinical data of UTI patients revealed a significant difference based on burning sensation, higher level was seen in the absence of burning. No other significant differences were found, as shown in Table (4.5). However, the mean level of SLPI was higher in patients with rUTI, presence of urgency, absence of suprapubic pain, continence urination, absence of hypertension, and unuse of antibiotics.

It has been documented that burning or pain during urination is typically caused by inflammation of the urethra or bladder. In women, inflammation in the vagina or in the region around the vaginal opening (called vulvovaginitis) can be painful when exposed to urine. Inflammation that results in burning or pain is usually caused by infection like UTI (Petersen & Naber, 2018). The presence of lower mean

in patients with burning sensation reflect the importance of SLPI role in inhibiting the inflammation during infection.

The studies have investigated the role of SLPI in UTIs, which revealed that SLPI levels may vary depending on the infection's severity and recurrence (Rosen *et al.,* 2023).

Table (4.5) Comparison between SLPI and Clinical Data of UTI patients.

Variables	N	Mean Rank	Mean ± SE	Mann Whitney Test / P- Value
Recurrent UTI:				
With rUTI	59	36.25	397.36±59.99	NS
Without rUTI	11	31.45	354.27±85.22	
Symptoms:				
1-Burning				
Present	61	33.51	376.95±58.54	0.033*
Absent	9	49.00	483.02±83.41	
2-Urgency				
Present	55	36.87	419.98±65.59	NS
Absent	15	30.47	282.81±24.97	
3-Frequency of Urination				
Present	51	34.90	387.78±66.50	NS
Absent	19	37.11	398.10±73.60	
4-Suprapubic Pain				
Present	53	32.96	328.07±25.99	NS
Absent	17	43.41	585.47±195.70	
Urination				
Continence	27	37.37	491.02±128.94	NS
Incontinence	43	34.33	327.52±23.73	
Hypertension				
Yes	14	30.57	296.06±27.14	NS
No	56	36.73	414.22±64.57	
Using Antibiotics				
Yes	22	35.59	353.67±52.59	NS
No	48	35.46	407.50±72.35	

N, Number; *, Significant at 0.05 level within UTI Patients; NS, Not Significant at 0.05 level; SLPI, Secretory Leukocyte Protease Inhibitor; SE, Standard Error; rUTI, Recurrent Urinary Tract Infection.

4.6. Laboratory Findings of UTI Patients and Healthy Controls.

4.6.1. Dipstick Results

The Table (4.6) represents data of the four subgroups based on dipstick results. No significant differences were found except for appearance of urine between

healthy controls subgroups, which might possibly reflect that dipstick parameter is not useful for UTI diagnosis. Forty-five of healthy group (64.3%) had turbid urine and among them 23 (51.1%) were ABU. Variations in urine appearance can arise due to factors like diet, hydration status, and specific medications. Evaluating urine appearance is an essential part of routine urinalysis, aiding in the early identification of potential health concerns (Zhang *et al.,* 2022).

The current study findings were also in line with the result of one study Mmoh *et al.,* (2022), in which (62.5%) of healthy females had abnormal urine appearance. This may be due to the presence of trace amounts of protein or other components that can cause urine to appear turbid (Mmoh *et al.,* 2022). Bacteria in the urine, sometimes without noticeable symptoms, can cause changes in urine appearance, such as increased turbidity (Ali *et al.,* 2024).

Table (4.6) Dipstick Results of UTI Patients and Apparently Healthy Controls.

Variable	UTI Patients		Total Number	Apparently Healthy Controls		Total Number	P - Value
	With bacterial growth	Without bacterial growth		With bacterial growth	Without bacterial growth		
N (%)	40(57.1)	30(42.9)	70(100.0)	28(40.0)	42(60.0)	70(100.0)	
Urine Color							
Yellow	37(55.2)	30(44.8)	67(95.7)	28(40.0)	42(60.0)	70(100.0)	NS
Other Color	3(100.0)	0(0.0)	3(4.3)	0(0.0)	0(0.0)	0(0.0)	
Chi-Square	NS			NS			-------
Appearance							
Clear	8(44.4)	10(55.6)	18(25.7)	5(20.0)	20(80.0)	25(35.7)	NS
Turbid	32(61.5)	20(38.5)	52(74.3)	23(51.1)	22(48.9)	45(64.3)	
Chi-Square	NS			0.012*			--------
PH							
From 4-6	37(56.9)	28(43.1)	65(92.9)	15(41.7)	21(58.3)	36(51.4)	0.000*
From 7-9	3(60.0)	2(40.0)	5(7.1)	13(38.2)	21(61.8)	34(48.6)	
Chi-Square	NS			NS			-------

N, Number; *, Significant at 0.05 level between UTI and Healthy Group; UTI, Urinary Tract Infection; NS, Not Significant at 0.05 level.

4.6.2. The Association Batween Means of pH Value and Bacteria Growth Among Studied Groups.

This study showed that healthy group had higher pH, as shown in Figure (4.1). The pH was significantly differed between patients and heathy. The mean pH of UTI patients with and without bacterial growth were (5.85±0.158), and (5.73 ± 0.106), respectively. Whereas the mean of pH value in healthy subjects with and without bacterial growth were (6.71±0.205) and (6.52±0.141), respectively. Inversely, Sokhn *et al.,* (2020) indicated that within UTI patients had the highest urine pH levels. Also, a previous study found no significant correlation between urine pH and the occurrence of UTIs (Hattah *et al.,* 2022). It has been documented that urine pH during UTIs is influenced by various factors, including the pathogenic characteristics of the infecting microorganism and the host's immune and physiological responses (Lai *et al.,* 2021). Diets can also influence urinary pH, and this effect depends on their ingredients and the balance between acidifiers and alkalizers (Queau, 2019).

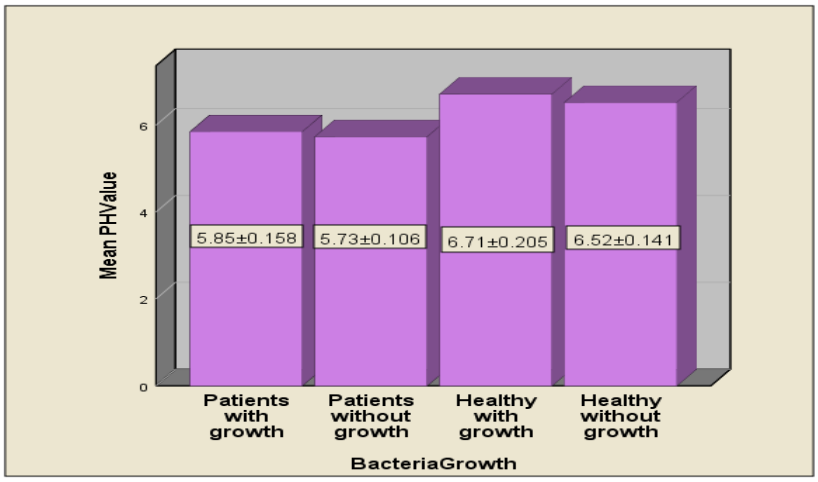


Figure (4.1): Association between pH Value and Bacteria Growth

4.6.3. General Urine Examination (GUE)

Based on GUE, there were significant difference among the four subgroups based on the presence of pus cells. Also, significant difference was found between

the two subgroups within healthy controls. A higher proportion of UTI patients with bacterial growth 29 (65.9%) had more than five pus cells. Also, ABU group had significant higher frequency of subject (57.6%) whom they had more than five pus cells compared to healthy group without bacterial growth (P- value, 0.007). In UTIs, increased pus cell counts result from an active immune reaction to infections (Ambite *et al.,* 2021). Analyzing test results, such as pus cell count, provide critical data for UTI diagnosis and severity evaluation (Sain & Dagar, 2024).

Bacteria that infect the kidney or bladder invade the mucous membrane and are attacked with a powerful host immune response. More pus cells show a strong immune response and also a high concentration of bacteria in infected patients because neutrophils, the first immune cells released, ingest bacterial cells then dying and becoming pus cell (Almaiman *et al.,* 2021). It was determined that bacteriuria was correlated to the presence of pus cells in the urine, with a high white blood cell count in the urine being the most reliable indicator for bacteriuria identification (Cheng *et al.,* 2022).

Furthermore, there were significant differences among the four subgroups regarding RBC counts. No significant difference was found regarding epithelial cells or the presence of bacteria in urine, as shown in Table (4.7). Some bacteria cause elevated RBC counts due to their virulence factors, which harm uroepithelial cells (Srinivasan *et al.,* 2025). A study conducted in Iraq concluded that elevated RBC counts in patients with UTIs result from an immune response that enhances leukocyte activity, which indirectly influences RBC levels by increasing vascular permeability (Ibrahim *et al.,* 2023).

Table (4.7) General Urine Examination of UTI Patients and Apparently Healthy Controls.

Variable	UTI Patients		Total Number	Apparently Healthy Controls		Total Number
	With bacterial growth	Without bacterial growth		With bacterial growth	Without bacterial growth	
N (%)	40(57.1)	30(42.9)	70(100.0)	28(40.0)	42(60.0)	70(100.0)
Pus Cell						
≤ Five	11(42.3)	15(57.7)	26(37.1)	9(24.3) [a]	28(75.7)	37(52.9)
> Five	29(65.9)	15(34.1)	44(62.9)	19(57.6)	14(42.4)	33(47.1)
Chi-Square	NS			0.007*		
Mean Rank	88.53	67.08 [a]	---------	82.59	47.71 [a]	---------
Mean ± SE	18.53±2.29	9.97±1.40		17.64±2.40	8.74±1.38	
Kruskal Wallis Test	0.000*					
RBC						
≤ Five	17(47.2)	19(52.8)	36(51.4)	17(22.7)	22(29.3)	39(55.7)
> Five	23(67.6)	11(32.4)	34(48.6)	11(16.9)	20(30.8)	31(44.3)
Chi-Square	NS			NS		
Mean Rank	86.94 [a]	70.08	---------	59.71	62.33	---------
Mean ± SE	9.25±1.50	6.87±1.39		4.79±0.55	5.43±0.65	
Kruskal Wallis Test	0.015*					
Epithelial Cell						
< twenty	20(52.6)	18(47.4)	38(54.3)	12(30.8)	27(69.2)	39(55.7)
≥ twenty	20(62.5)	12(37.5)	32(45.7)	16(51.6)	15(48.4)	31(44.3)
Chi-Square	NS			NS		
Mean Rank	71.16	66.60	---------	84.96	63.01	---------
Mean ± SE	16.13±1.70	14.77±1.79		19.86±2.16	13.69±1.40	
Kruskal Wallis Test	NS					
Bacteria Seen in Urine						
Seen	22(68.8)	10(31.1)	32(45.7)	13(43.3)	17(56.7)	30(42.9)
No Seen	18(47.4)	20(52.6)	38(54.3)	15(37.5)	25(62.5)	40(57.1)
Chi-Square	NS			NS		

N, Number; *, Significant at 0.05 Level between UTI and Healthy Group; NS, Not Significant at 0.05 level; UTI, Urinary Tract Infection; RBC, Red Blood Cell; SE, Standard Error; [a], Values Differ Significantly at 0.05 Level within UTI and Healthy Subgroups.

4.6.4. Urine Cultures

Among the 140 participants, 40 (57.1%) of UTI patients had positive growth whereas 28 (40.0%) of healthy group had positive growths (ABU). *E. coli* was the most common pathogen in both UTI patients (52.5%) and ABU (46.4%) cases followed by *S. saprophyticus* (32.5% and 32.1%) and *S. epidermidis* (10.0% and 14.3%) in UTI patients and ABU, respectively. In a study conducted in Babylon

city in Iraq, the same results were found, *E.coli* was the most prevalent bacterium at (48%), followed by *K. pneumoniae* at (17.4%) and *S. saprophyticus* at (10%) (Ali & Aljanaby, 2023). In another study, it was found that the primary isolate was *E. coli*, at a percentage of (65.84%) (Sharmin *et al.,* 2022).

Gram-negative bacteria represent a major global public health concern, particularly in UTIs, due to their high antibiotic resistance (Oliveira & Reygaert, 2019). Extensive study and classification of *E. coli* strains have shown their ability to cause a variety of diseases. Their virulence enables them to evade the host's immune defenses and develop resistance to commonly used antibiotics (Mueller & Tainter, 2023). Gram-positive bacteria, such as *S. saprophyticus*, are commonly responsible for UTIs, particularly in young sexually active women. Additionally, they can cause less common but serious conditions, including acute pyelonephritis, urethritis, epididymitis, and prostatitis (Argemi *et al.,* 2019).

Table (4.8) Urine Cultures of UTI patients and Asymptomatic Bacteriuria.

Variable	UTI Patients With bacterial growth	ABU	Chi-Square
	N (%)	N (%)	
Isolated Organism			
Escherichia coli	21(52.5)	13(46.4)	NS
Staphylococcus saprophyticus	13(32.5)	9(32.1)	
Staphylococcus epidermidis	4(10.0)	4(14.3)	
Enterobacter*, *Staphylococcus. Suis, klebsiella. pneumonia.	2(5.0)	2(7.1)	
Total Number	40(100.0)	28(100.0)	

N, Number; NS, Not Significant at 0.05 level; UTI, Urinary Tract Infection; ABU, Asymptomatic Bacteriuria

4.7. The Sensitivity and Specificity, Positive and Negative Predictive Value of Urinalysis in UTI Patients and Apparently Healthy Control

The sensitivity, PPV and NPV were calculated for pH and GUE parameters, as shown in Table (4.9). The results showed that the higher sensitivity was seen for the presence of pus cells in urine of the patients (72.5). This might be due to the immune response, as neutrophils, which fight bacteria in the urinary tract, resulting

in an elevated presence of pus cells in urine (Ibrahim *et al.,* 2023). High sensitivity is essential for screening tests to reduce false negatives (Monaghan *et al.,* 2021). PPV (was for bacterial presence in urine) and NPV (was seen for pus cells) were ranged from (60-68.7) and (43-57.7), respectively. As shown in Table (4.10), The highest specificity, PPV and NPV of urinary parameters tests for healthy control was seen for the presence of pus cells. High specificity is crucial for minimizing false positives and preventing the misdiagnosis of healthy individuals (Monaghan *et al.,* 2021).

PPV and NPV are influenced by disease prevalence; higher prevalence leading to increase both PPV and NPV (Gogtay & Thatte, 2017). A study reported that the PPV for detecting significant presence of bacteria in urine ranged from (67%) to (73%) across different culture thresholds (Gehringer *et al.,* 2021). However, despite NPV is useful, the presence of pus cells alone does not confirm infection, and additional diagnostic tests may be necessary to prevent misdiagnosis (Rothe *et al.,* 2020).

Table (4.9) The Sensitivity, PPV and NPV of Urinalysis in UTI Patients.

Test Result	With bacterial growth N (%)	Without bacterial growth N (%)	Sensitivity (%)	PPV (%)	NPV (%)
Total Number	40(57.1)	30(42.9)			
Dipstick:					
PH					
From 4-6	37(92.5)	28(93.3)	7.5	60.0	43.0
From 7-9	3(7.5)	2(6.7)			
GUE:					
1-Pus Cell					
> Five	29(72.5)	15(50.0)	72.5	65.9	57.7
≤ Five	11(27.5)	15(50.0)			
2-RBC					
> Five	23(57.5)	11(36.7)	57.5	67.6	52.8
≤ Five	17(42.5)	19(63.3)			
3-Epitheilal Cell					
≥ Twenty	20(50.0)	12(40.0)	50.0	62.5	47.4
< Twenty	20(50.0)	18(60.0)			
4-Bacteria Seen					
Seen	22(55.0)	10(33.3)	55.0	68.7	52.6
No Seen	18(45.0)	20(66.7)			

UTI, Urinary Tract Infection; N, Number; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

Table (4.10) The Specificity, PPV and NPV of Urinalysis in Apparently Healthy Control.

Test Result	With bacterial growth N (%)	Without bacterial growth N (%)	Specificity (%)	PPV (%)	NPV (%)
Total Number	28(40.0)	42(60.0)			
Dipstick:					
PH					
From 4-6	15(53.6)	21(50.0)	50.0	38.2	58.3
From 7-9	13(46.4)	21(50.0)			
GUE:					
1-Pus Cell					
> Five	19(67.9)	14(33.3)	66.7	57.6	75.7
≤ Five	9(32.1)	28(66.7)			
2-RBC					
> Five	11(39.3)	20(47.6)	52.4	35.5	56.4
≤ Five	17(60.7)	22(52.4)			
3-Epitheilal Cell					
≥ Twenty	16(57.1)	15(35.7)	64.3	51.6	69.2
< Twenty	12(42.9)	27(64.3)			
4-Bacteria Seen					
Seen	13(46.4)	17(40.5)	59.5	43.3	62.5
No Seen	15(53.6)	25(59.5)			
N, Number; PPV, Positive Predictive Value; NPV, Negative Predictive Value.					

4.8. Pus / Epithelial Cells Dual Presence

4.8.1. Pus / Epithelial Cells Dual Presence in UTI Patients

As shown in Table (4.9), 28 (59.6%) patients were with true infections, and 12 (52.2%) were considered as contamination. However, 19 (40.4%) of urine samples that were without growth might possibly have true infection. The sensitivity, specificity, PPV and NPV were (70.0%), (50.0%), (65.1%), and (55.6%), respectively.

The presence of pyuria (pus cell in urine) aids in confirming the diagnosis of UTI in patients presenting with typical clinical symptoms and signs. Additionally, urinalysis has been found to be an effective "rule-out" test for UTI (Advani *et al.,* 2024). A presence of ≥ 5 pus cells per HPF is typically regarded as indicative of a UTI (Thyagaraju et al., 2024). Epithelial cells can be further divided into squamous and transitional types. While these sub-classifications are clinically significant, they are rarely included in routine urine diagnostic reports. The normal range for

epithelial cells is 0-15 per HPF. An elevated count suggests inflammation in the urinary tract (Goswami *et al.,* 2021).

There wasn't previous study that focused on dual presence of both pus and epithelial cells. Also, to facilitate the results interpretation of positive bacterial growth and exclude contamination using GUE, this study investigated the pus / epithelial cell dual presence (PEDP) and study their impact on diagnosis of UTI based on urine culture. PEDP was calculated as the dual presence of high number of pus (>5 cells /HPF) and epithelial cells (>20 cells/ HPF) might be considered as strong indicator of true infection while if one of them present might possibly regarded as contamination.

Sensitivity is the capacity to test positive when bacteriuria is substantially present. While specificity is the measure of the capacity to test positive for bacteriuria and no other cause (Zenoh *et al.,* 2018). As the risk of contamination is high, and operator errors can lead to unreliable urine collection, particularly during the preanalytical phase of urine culture. Proper use of urine culture helps address these issues and aids in managing this common infection (Sinawe & Casadesus, 2020).

Urinary symptoms alone are not highly accurate in diagnosing culture-positive UTIs. However, the diagnostic accuracy improves when urine microscopy detects pyuria and/or an elevated bacterial count (Tan *et al.,* 2019). Urine culture is complex and prone to contamination by various bacteria (Xie *et al.,* 2022). Factors such as a high BMI, the time since the last shower, or the extent of intimate hair removal could potentially contribute to urine sample contamination (Pernille *et al.,* 2019).

Table (4.11) Pus / Epithelial Cells Dual Presence in UTI Patients.

Variables	With Growth N (%)	Without Growth N (%)	Chi-Square/	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total Number	40(57.1)	30(42.9)					
PEDP							
True Infection	28(59.6)	19(40.4)	NS	70.0	50.0	65.1	55.6
contamination	12(52.2)	11(47.8)					

N, Number; NS, Not Significant at 0.05 level; PPV, Positive Predictive Value; NPV, Negative Predictive Value; PEDP, Pus / Epithelial cell dual presence;

4.8.2. Pus / Epithelial Cells Dual Presence in Apparently Healthy Controls with and without Asymptomatic Bacteriuria

As shown in Table (4.12), PEDP was found in 30 subjects from total healthy group (42.9%). However, 14 of them (46.7%) had positive bacterial growth and 16 (53.3%) were without growth. The sensitivity, specificity, PPV, and NPV were (67.9%), (64.3%), (55.9%), and (75.0%), respectively. ABU is characterized by the presence of $>10^5$ bacteria/mL in urine, with or without pyuria. Patients with the ABU strain may harbor pathogens for months or even years without exhibiting any symptoms. study has demonstrated that ABU provides protection to the host against symptomatic UTIs (Wullt & Svanborg, 2016).

Dietary factors, such as sodium intake and hydration levels, can greatly influence urinary composition, causing elevated parameters even without the presence of infection (Liu *et al.,* 2023). Pyuria is a general indicator of inflammation in the genitourinary tract. It commonly occurs alongside ABU, and its frequency differs across various bacteriuric individuals (Nicolle, 2016). A study concluded that the presence of epithelial cells slightly reduced the predictive accuracy of positive culture results, also these contaminating cells from the urogenital surface can affect the reliability of other urinary inflammatory markers, such as pus cells (Maher *et al.,* 2020).

Table (4.12) Pus / Epithelial Cells Dual Presence in Apparently Healthy Control with and without Asymptomatic Bacteriuria.

Variables	With Growth N (%)	Without Growth N (%)	Chi-Square	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total Number	28(40.0)	42(60.0)					
PEDP							
True Infection	14(46.7)	16(53.3)	NS	67.9	64.3	55.9	75.0
contamination	14(35.0)	26(65.0)					

N, Number; NS, Not Significant at 0.05 level; PPV, Positive Predictive Value; NPV, Negative Predictive Value; PEDP, Pus / Epithelial cell dual presence.

4.9. Association between SLPI and Laboratory Findings

4.9.1. Association between SLPI and Dipstick Characteristics.

As shown in Table (4.13), the mean level of serum SLPI was compared between the two groups according to dipstick findings. The mean ± SE values for SLPI in both UTI and control were approximately similar. There was no statistically significant difference in the color and appearance of urine between the two groups. The color of urine serves as a reliable indicator of the affected body fluid; for example, yellow urine indicated the presence of bile. Analyzing urine provided an objective approach to diagnosis (McIntire *et al.,* 2020). Certain foods and medications can influence the color, odor, or pH level of urine. Sample contamination or the presence of pathogenic bacteria may lead to misleading results, potentially shifting the specimen's pH toward acidity or alkalinity (Milani & Jialal, 2023).

There was significant difference in SLPI level between the two studied groups according to pH categories and also within control group. The results of this study showed that within acidic urine the serum SLPI level was lower than that of alkaline pH urine which appears to duplicate the SLPI serum level in UTI patients. However, inverse relation was seen in healthy group in which the level of SLPI was higher in acidic urine category. It has been documented that SLPI defends against uropathogen-induced UTIs by boosting immune responses and lowering bacterial levels in the bladder. The impact of urinary pH on SLPI expression and function still

remains need more clarification. Rosen *et al.,* (2023) documented that an acidic environment might affect SLPI's antimicrobial activity, but more study is required to better understand this connection.

Table (4.13) Association between SLPI and Dipstick Characteristics of UTI Patients and Apparently Healthy Control.

Variables	UTI Patients			Apparently Healthy Control			Mann Whitney Test
	N	Mean Rank	Mean ± SE	N	Mean Rank	Mean ± SE	
Urine Color							
Yellow	67	35.64	394.47±54.42	70	35.30	390.35±40.18	NS
Other Color	3	32.33	303.81±41.50		----------	----------	--------
Kruskal Wallis Test/ P- Value	NS			----------			--------
Appearance							
Clear	18	31.33	300.36±24.59	25	32.56	369.41±47.68	NS
Turbid	52	36.94	421.82±69.34	45	37.13	401.98±56.92	NS
Kruskal Wallis Test/ P- Value	NS			NS			---------
pH							
From 4-6	65	34.32	368.91±53.29	36	40.33	452.88±72.31	0.03*
From 7-9	5	50.80	672.35±210.84	34	30.38	324.16±28.61	0.02*
Kruskal Wallis Test/ P- Value	NS			0.041*			------

N, Number; *, Significant at 0.05 level between UTI and Healthy Group; NS, Not Significant at 0.05 level; SLPI, Secretory Leukocyte Protease Inhibitor; SE, Standard Error; UTI, Urinary Tract Infection.

4.9.2. Association between SLPI and General Urine Examinations.

The results in Table (4.14) indicate that there were no significant differences ($P > 0.05$) in the mean level of SLPI according to GUE between the studied groups. The mean level was higher in the group with >five pus cells, ≤ 5 RBCs and in ≤ twenty epithelial cells in UTI patients. Inversely, higher mean was seen in healthy group with > 5 RBCs and in > twenty epithelial cells. There were significant and marginally significant increase in the mean of SLPI within healthy group according to the presence of bacteria in urine and the count of epithelial cells, respectively. The diagnostic accuracy of UTI screening through urine test strip analysis and microscopic examination is less than optimal (Mattoo & Spencer, 2024). Pus cell levels may be affected by factors like recent antibiotic treatment or other urinary

disorders, which can make the diagnosis more challenging (Liu *et al.,* 2024). There are limited studies on the relationship between SLPI levels and UTIs, with most of them concentrating on acute kidney injury following surgery and assessing the condition before and after renal transplantation (Averdunk *et al.,* 2019, 2020).

Table (4.14) Association between SLPI and General Urine Examinations of UTI Patients and Apparently Healthy Control.

Variables	UTI Patients			Apparently Healthy Control			Mann Whitney Test/P- Value
	N	Mean Rank	Mean ± SE	N	Mean Rank	Mean ± SE	
Pus Cell							
≤ Five	26	36.35	341.34±32.35	37	33.62	355.66±32.87	NS
> Five	44	35.00	419.68±80.80	33	37.61	429.24±77.01	NS
Kruskal Wallis Test/ P- Value	NS			NS			---------
RBC							
≤ Five	36	37.39	432.06±94.00	39	37.18	388.01±34.03	NS
> Five	34	33.50	346.67±40.84	31	33.39	393.29±80.86	NS
Kruskal Wallis Test/ P- Value	NS			NS			-------
Epithelial Cell							
< Twenty	38	34.13	414.62±90.55	39	31.33	341.94±30.96	NS
≥ Twenty	32	37.13	362.04±39.61	31	40.74	451.25±81.45	NS
Kruskal Wallis Test/ P- Value	NS			0.055**			-------
Bacteria Seen in Urine							
Seen	32	36.75	347.80±35.03	30	41.03	469.31±86.08	NS
No Seen	38	34.45	426.61±91.64	40	31.35	331.13±25.62	NS
Kruskal Wallis Test/ P- Value	NS			0.049*			------

N, Number; *, Significant at 0.05 level between UTI and Healthy Group; NS, Not Significant at 0.05 level; **, Marginal Significant at 0.05 level; SLPI, Secretory Leukocyte Protease Inhibitor; SE, Standard Error; UTI, Urinary Tract Infection.

4.9.3. Association between SLPI and Culture Results.

Comparison the mean level of SLPI according to culture status of urines revealed non-significant difference between the two study groups, as shown in Table (4.15). Non-significant higher mean of SLPI was noticed in UTI patients whom they did not have positive bacterial growth category but for healthy group, higher mean was noticed in ABU group. This might reflect the importance of SLPI in fighting bacterial infections, since presence of lower level of SLPI makes the female more

susceptible to bacterial infection. In a mouse model study, it has been documented a lack of SLPI results in higher bacterial loads and increased inflammation (Rosen *et al.,* 2023). In study conducted on lab animals and measured the level of SLPI in urine showed the level of SLPI in urine is closely linked to the bacterial load (Rosen, 2021).

In this study, higher mean level in UTI patients was seen with *S. epidermidis*. On the other hand, the higher mean in ABU was seen with *E. coli*. A previous study revealed that SLPI functions as both an antimicrobial and immunomodulatory agent, with its levels significantly elevated in blood stream infections caused by *S. pneumoniae* and *S. aureus* compared to *E.coli* (Lange *et al.,* 2019). The presence of specific bacteria is associated with increased inflammatory markers, which may influence SLPI levels and modulating the overall immune response (AL-Khikani *et al.,* 2019). The antimicrobial role of SLPI has been reported against *E.coli, P. aeruginosa, S. aureus,* and *S. epidermidis* (Majchrzak-Gorecka *et al.,* 2016).

Table (4.15) Association between SLPI and Culture Results of UTI Patients and Apparently Healthy Control.

Variables	UTI Patients			Apparently Healthy Control			Mann Whitney Test/P-Value
	N (%)	Mean Rank	Mean ± SE	N (%)	Mean Rank	Mean ± SE	
Bacteria Growths							
with Growth	40(57.1)	36.55	380.87±41.15	28(40.0)	32.75	413.11±90.84	NS
Without Growth	30(42.9)	34.10	403.54±109.76	42(60.0)	37.33	375.18±29.86	NS
Kruskal Wallis Test/ P-Value	NS			NS			------
Isolated Organism							
Escherichia coli	21(52.5)	35.90	375.27±56.33	13(46.4)	36.92	523.77±190.56	NS
Staphylococcus saprophyticus	13(32.5)	36.15	374.43±71.13	9(32.1)	22.44	269.03±30.78	NS
Staphylococcus epidermidis	4(10.0)	56.75	550.57±153.63	4(14.3)	52.00	468.13±81.29	NS
Enterobacter,Staphylococcus. Suis, klebsiella. pneumonia	2(5.0)	5.50	142.16±58.39	2(7.1)	13.50	232.08±34.44	NS
None	30(100.0)	34.10	403.54±109.76	42(100.0)	37.33	375.18±29.86	NS
Kruskal Wallis Test/ P-Value	NS			0.059**			---------

N, Number; *, Significant at 0.05 level; NS, Not Significant at 0.05 level; **, Marginal Significant at 0.05 level; SLPI, Secretory Leukocyte Protease Inhibitor; SE, Standard Error; UTI, Urinary Tract Infection.

4.10. Association between SLPI and Gathering GUE Test Results.

4.10.1. The Distribution of Gathering GUE Test Results in UTI Patients

As shown in Figure (4.2), there were 10 (14.3 %) of UTI patients who had pus, epithelium, RBCs, and bacteria seen according to GUE. Whereas, 16 (22.9%) had negative results for these tested parameters. Eleven patients (15.7%) had Pus, Epithelium, and bacteria seen in Urine. There were 7 (10.0%) of female patients who had pus and RBC cells in the results of GUE. It has been documented that the presence of urinary parameters is essential for diagnosing UTIs. However, their presence alone does not always justify antibiotic treatment. Consistent monitoring of these indicators can help prevent recurrent infections and manage complications, especially in high-risk groups (Al Lawati *et al.,* 2024). A study observed that there was a correlation between pus cell count, bacteria seen in urine, and the pH of the corresponding isolates from patients with UTI (Oluwafoise, 2019). Kim *et al.,* (2021) revealed that the urinary parameters like RBC, WBC, epithelial cell and bacteria seen microscopically were statistically associated with positive urine cultures.

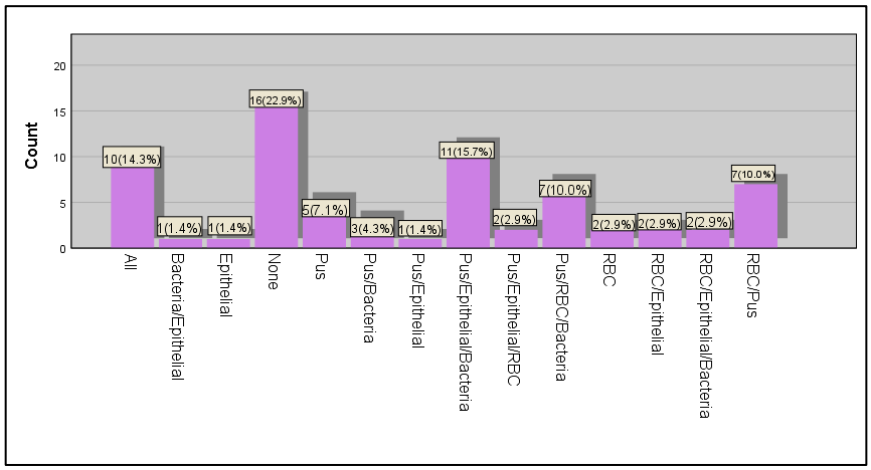


Figure (4.2): The Distribution of Gathering GUE Test Results Among UTI Patients.

4.10.2. The Distribution of Gathering GUE Test Results in Apparently Healthy Female.

As displayed in Figure (4.3), there were 11 (15.7 %) of apparently healthy female had negative results for GUE tested parameters. Five of subjects (7.1%) had pus, epithelium, RBCs, and bacteria seen according to GUE. There were 12 (17.1%) had elevated RBCs seen in Urine. Nine of healthy female (12.9%) had pus, epithelial cells and bacteria seen in urine analysis. ABU is characterized by the presence of significant bacteriuria without symptoms; however, the presence of urinary parameters can resemble UTI, making diagnosis more challenging (Basumatary *et al.,* 2020). A study concluded that participants lacking classic UTI symptoms who had a positive urinalysis should not automatically undergo urine culture testing or receive antibiotic therapy. Instead, clinical judgment should be applied (Thyagaraju *et al.,* 2024).

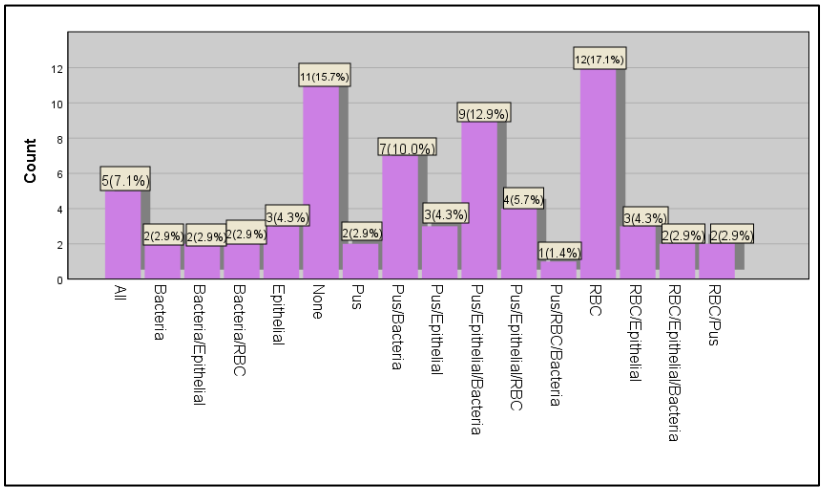


Figure (4.3): The Distribution of Gathering GUE Test Results in Apparently Healthy Female.

4.10.3. Distribution of Gathering GUE Test Results between Study Groups.

There was a significant difference in distribution of patients and control groups according to probability of having positive test results from the tested variables, as shown in Table (4.16). Four positives meaning the participant had elevated variables (pus cells, RBC, epithelial cell, and the bacteria was seen

microscopically). Twenty-seven (16, 22.9%) from UTI patients and 11 (15.7%) from healthy control) had normal results for all tested variables. However, 10 (14.3%) from UTI and 5 (7.1%) from healthy had four positive results. the variation in probability could be attributed to host susceptibility, which is partly due to weaknesses in the innate immune system, creating opportunities for invading pathogens (Telenti & di Iulio, 2020). A positive test result may raise the probability of a UTI. When the probability of infection is moderate or uncertain, a urine culture should be conducted (Chu & Lowder, 2018). The combined impact of fluctuating bacteriuria prevalence and differing diagnostic values caused significant variation in the probability of bacteriuria when symptoms were considered together (Holm *et al.,* 2021).

Table (4.16) Distribution of Gathering GUE Test Results Among the Study Groups.

Variable	UTI Patients		Total Number 70(100.0)	Apparently Healthy Female		Total Number 70(100.0)	Chi-Square
	With bacterial growth	Without bacterial growth		With bacterial growth	Without bacterial growth		
	N (%)			N (%)			
Probability							
Four Positive	7(46.7)	3(20.0)	10(14.3)	3(20.0)	2(13.3)	5(7.1)	0.027*
Three Positive	14(36.8)	8(21.1)	22(31.4)	8(21.1)	8(21.1)	16(22.9)	
Two Positive	10(30.3)	4(12.1)	14(20.0)	8(24.2)	11(33.3)	19(27.1)	
One Positive	4(14.8)	4(14.8)	8(11.4)	7(25.9)	12(44.4)	19(27.1)	
All Normal	5(18.5)	11(40.7)	16(22.9)	2(7.4)	9(33.3)	11(15.7)	
P-Value	0.149			0.434			

UTI, Urinary Tract Infection; N, Number; *, Significant at 0.05 level; Four Positive, Elevated All the Variables (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically); Three Positive, Elevated Three from the Following (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically); Two Positive, Elevated Two from the Following (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically); One Positive, Elevated One from the Following (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically); All Normal, No Elevated from the Following (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically).

4.10.4. The Comparison of SLPI with Urinalysis Among Study Groups.

Table (4.17) represents the comparison of SLPI mean level according to the probability of having positive test results between UTI patients and healthy control. The mean of SLPI was significantly higher in healthy control, (P = 0.014) than patients with UTI whom they had four positive test results (four positives meaning the participant had elevated variables like pH, pus cells, RBC, epithelial cell, and the

bacteria was seen microscopically). No other significant results were seen. The presence of lower mean of SLPI in UTI patients might possibly reflect the importance of SLPI in innate immune response and defending against bacterial infection and the lack of it or its presence in low level increase host susceptibility to infection. SLPI has been demonstrated to suppress the production of pro-inflammatory cytokines in cells triggered by lipopolysaccharides, thereby effectively reducing inflammation (Douglas & Hannila, 2022).

SLPI plays a crucial role in preventing the invasion of pathogenic bacteria. Primarily produced at mucosal surfaces, SLPI acts as a defense mechanism against microbial infections by inhibiting proteases and modulating immune responses (Ozaka *et al.,* 2021). SLPI not only contributes to pathogen defense but also plays a key role in regulating inflammation and supporting cell proliferation in various tissues and organs (Munn & Garkavtsev, 2018). No previous study was found that investigate the association between gathering GUE test results and SLPI in females with UTI and healthy group.

However, SLPI has been identified as a significant marker in kidney diseases, particularly acute kidney injury (AKI). Studies have shown that both SLPI mRNA and protein levels in serum and urine are linked to the early detection of AKI. Additionally, urinary SLPI levels correlate with organ damage. From a therapeutic perspective, SLPI has demonstrated beneficial effects by reducing creatinine levels, inflammation, and cell apoptosis in models of ischemia/reperfusion injury (Mongkolpathumrat *et al.,* 2024).

Table (4.17) Association between SLPI and Probability of UTI Patients and Apparently Healthy Female.

Variables	UTI Patients			Apparently Healthy Female			Kruskal Wallis Test/ P- Value
	N	Mean Rank	Mean ± SE	N	Mean Rank	Mean ± SE	
Probability							
Four Positive	10	6.00	245.87±30.23	5	12.00	855.35±483.45	0.014*
Three Positive	22	18.05	384.30±46.43	16	21.50	394.43±33.25	NS
Two Positive	14	18.29	428.07±88.19	19	16.05	319.10±26.61	NS
One Positive	8	15.63	722.96±406.94	19	13.32	329.48±46.76	NS
All Normal	16	12.56	290.69±19.56	11	16.09	401.27±75.00	NS

N, Number; *, Significant at 0.05 level; NS, Not Significant at 0.05 level; SLPI, Secretory Leukocyte Protease Inhibitor; SE, Standard Error; UTI, Urinary Tract Infection; Four Positive, Elevated All the Variables (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically); Three Positive, Elevated Three from the Following (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically); Two Positive, Elevated Two from the Following (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically); One Positive, Elevated One from the Following (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically); All Normal, No Elevated from the Following (pus cells, RBC, epithelial cell, and the bacteria was seen microscopically).

4.11. Association of SLPI Quartiles with Culture Positivity and RUTI History.

Cross tabulation between SLPI quartiles frequencies and the presence or absence of both culture and history of rUTI was analyzed and the results indicate that the highest frequency of both patients and control whom they had of the culture negative with rUTI. Approximately 25 (58.1%) of both patients and control had culture negative and positive rUTI and had higher SLPI in third quartile (Q3). This may reflect that either recurrent infection may cause increase level of SLPI that affect the bacteria and thus no bacterial growth was found in culture or due to the presence of continuous inflammatory response that require increase level of SLPI, as shown in Figure (4.4).

In a recent study on diabetic kidney disease, serum SLPI levels were divided into quartiles. Patients in the third quartile (Q3) showed a significantly higher rate of disease progression compared with those in the lowest quartile (Q1), indicating that elevated SLPI levels (such as in Q3) are associated with increased risk of disease advancement (Sun *et al.,* 2024).

Women with a history of rUTI and a culture positive for the presence of a uropathogen did not show increased SLPI levels compared to those with a negative culture, indicating that SLPI expression may be disrupted in these cases (Rosen *et al.,* 2024). Recent study indicates that the urobiome (a diverse population of microorganisms residing in the urinary tract) may significantly contribute to the onset and recurrence of UTIs (Wolfe & Brubaker, 2019). Innate immune cells like neutrophils and macrophages play a crucial role in defending against uropathogenic bacteria. They secrete cytokines and chemokines that attract more immune cells to the site of infection (Naskar & Choi, 2024).

No previous study was investigate the association between frequencies of SLPI quartiles with culture positivity and rUTI in females. Sawicki *et al.,* (2023) investigates association of serum SLPI levels with onset of heart failure, The incidence rate was highest among participants in the highest quartile of serum SLPI. Infections can cause persistent changes in the urothelium, increasing its susceptibility to subsequent infections. This process of tissue remodeling plays a key role in the recurrence of UTIs (Lacerda Mariano & Ingersoll, 2020).

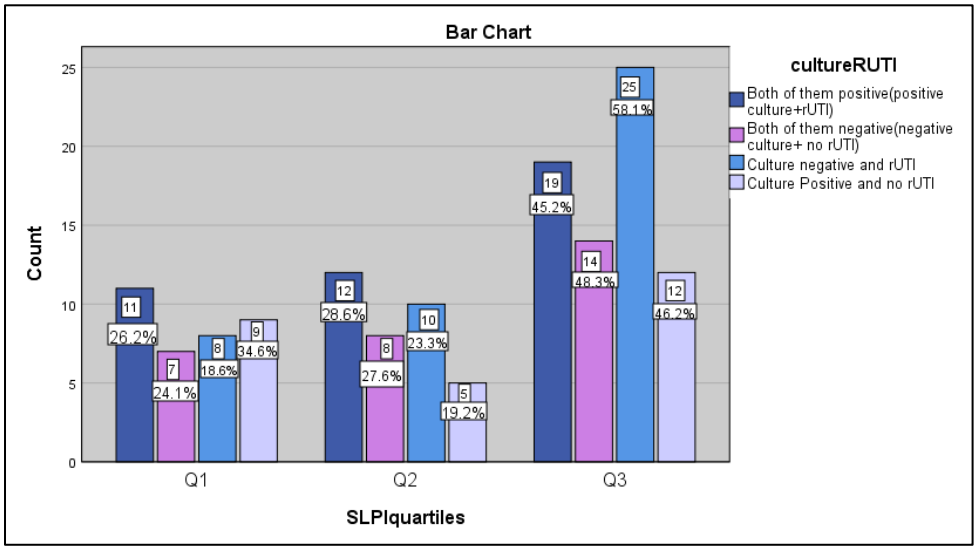


Figure (4.4): Association of SLPI Quartiles with Culture Positivity and RUTI History.

4.12. Correlation of SLPI With Tested Parameters.

Correlation analysis of this study revealed that there was no significant correlation between the SLPI mean level and the tested parameters within urinalysis, as shown in Table (4.18). No previous study investigated the correlation between SLPI and urinalysis parameters. However, a study conducted in patients with diabetic kidney disease found a positive correlation between serum SLPI levels and disease progression (Sun *et al.,* 2024). Patients who developed acute kidney infections showed markedly elevated serum SLPI levels. Study exploring SLPI's role in organ injury consistently highlights its protective effects, primarily through its ability to regulate inflammatory responses (Averdunk *et al.,* 2020).

Table (4.18): Correlation of SLPI With Tested Parameters.

variable	SLPI		
	N	Pearson Correlation	Sig. (2-tailed)
PH Value	140	0.046	0.587
RBC Value	140	-0.058	0.499
Pus Value	140	0.131	0.122
Epithelial Value	140	0.031	0.715
PEDP	140	-0.059	0.487
N, Number; RBC, Red Blood Cell; PEDP, Pus Epithelial Dual Presence; Sig, Significance.			

4.13. Receiver Operating Characteristic Curve (ROC) for the Studied Variables.

The ROC curve is used to determine a patient's disease status as either positive or negative based on test results. It also assesses the overall diagnostic effectiveness of a test and allows for the comparison of multiple tests' performance (Nahm, 2022). In the current study, the ROC was analyzed to determine the performance of the tested variable including, PH values, pus cells, RBC, epithelial cell, SLPI, and PEDP in diagnosing UTI patients from healthy individuals. The results revealed that the area under curve (AUC) for PH, pus cells, RBC, PEDP, SLPI, and epithelial cell (0.737), (0.626), (0.632) and (0.648), (0.542) and (0.518), respectively, as shown in Figures (4.5-10). PH value had the highest discriminatory power in discrimination

of UTI patients and healthy individuals. Followed by RBC, and Pus cells. The SLPI had poor prognostic ability. PEDP had higher AUC than pus cell alone.

High pus cell counts are linked to typical UTI symptoms like painful urination and frequent urges to urinate, highlighting their importance diagnostic value in UTI (Sain & Dagar, 2024). Previous study reported that the ROC curve for the pus cell was (AUC=0.779; 95% CI=0.769–0.789) therefore, suggested that this parameter had important diagnostic value for UTIs (Kim *et al.,* 2021). Another study documented that the AUC for RBC was (AUC = 0.72) (Foudraine *et al.,* 2018).

There is a little information about the utility of using SLPI serum level as a diagnostic biomarker in the diagnosis of UTI. However, a study conducted by Afacan *et al.,* (2022) showed that salivary levels of SLPI had good diagnostic values in identifying individuals with periodontitis, an AUC value of (0.82).

The pH of urine remains stable when it is sterile, but it changes as a result of bacterial UTIs (Nwamaka *et al.,* 2025). It has been documented that the AUC for urinary pH in patients with urinary tract stone was (0.77) (Kim *et al.,* 2019).

Epithelial cells in the urinary tract react responses to bacterial colonization through a complex interaction of cellular and molecular processes. These responses are essential for realizing infection dynamics and predicting potential infections (Khasriya *et al.,* 2013). The existence of intracellular bacterial reservoirs and the capacity of epithelial cells to influence immune responses emphasize the necessity for more advanced diagnostic methods beyond standard cultures (Brannon *et al.,* 2020). Mohr *et al.,* (2016) found the AUC for urinary epithelial cell was at about (0.68). The differences in the results of the current study in comparison to the mentioned studies might possibly due to the differences in study design, the type of patients included, type of samples, size of samples and geographic area of studies.

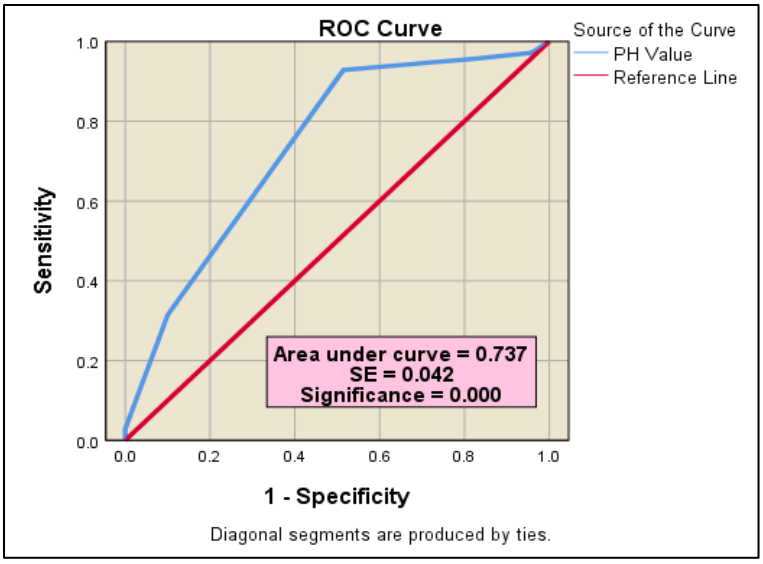


Figure (4.5): Receiver Operating Characteristic Curve and Area Under the ROC of pH Value Result (UTI Patients vs Asymptomatic Bacteriuria).

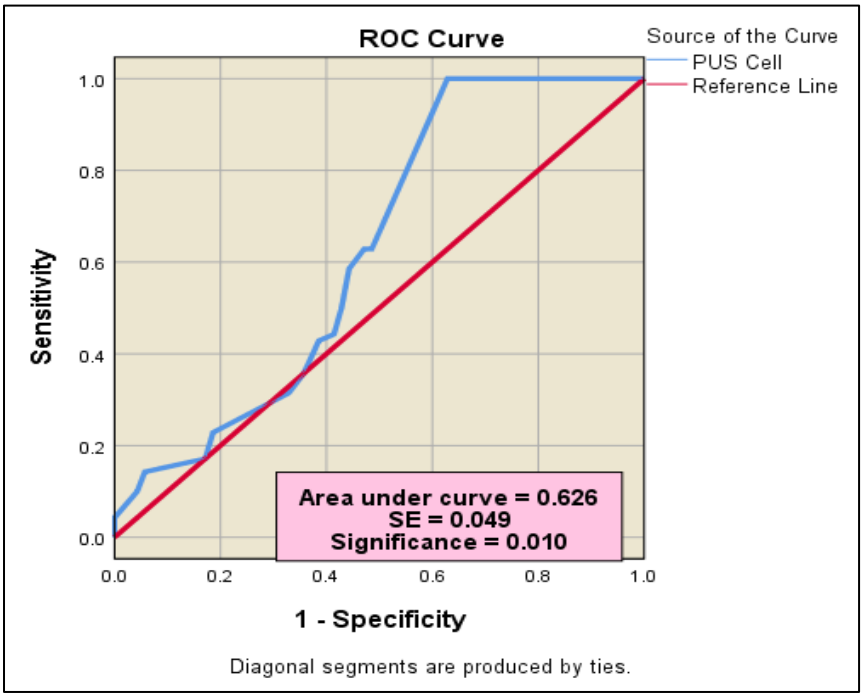


Figure (4.6): Receiver Operating Characteristic Curve and Area Under the ROC of Pus Cell (UTI Patients vs Asymptomatic Bacteriuria).

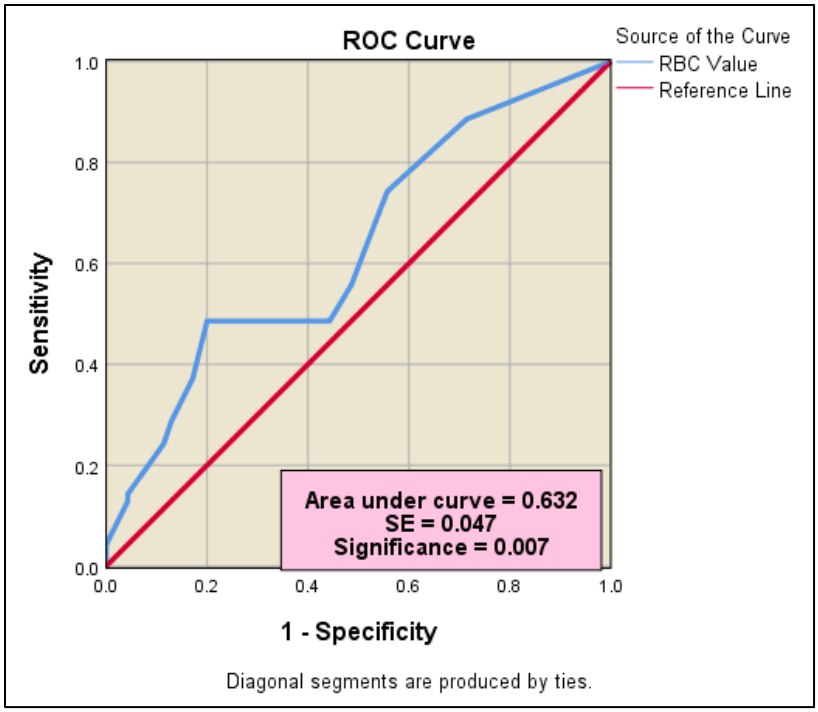


Figure (4.7): Receiver Operating Characteristic Curve and Area Under the ROC of RBC Cell (UTI Patients vs Asymptomatic Bacteriuria).

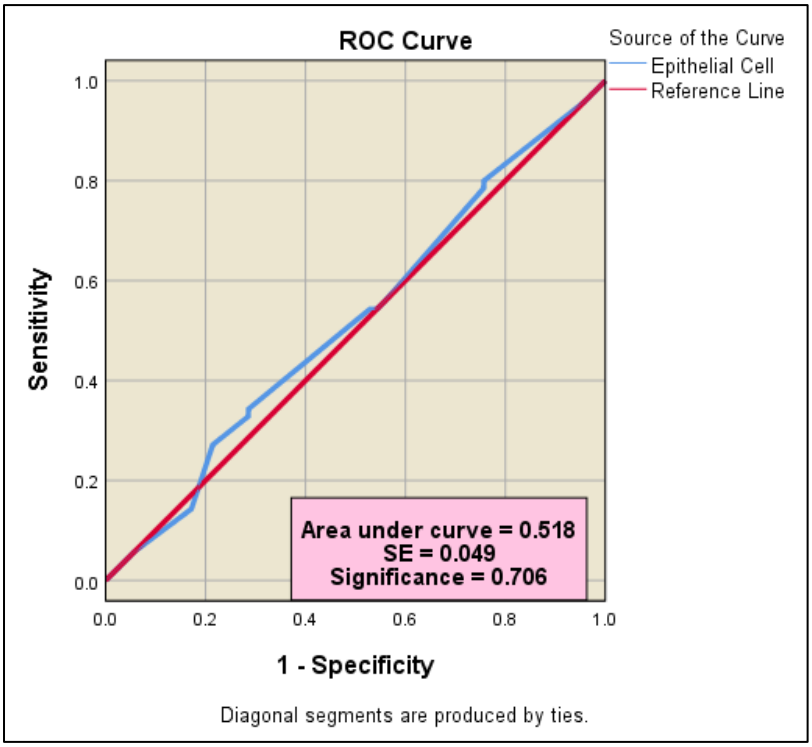


Figure (4.8): Receiver Operating Characteristic Curve and Area Under the ROC of Epithelial Cell (UTI Patients vs Asymptomatic Bacteriuria).

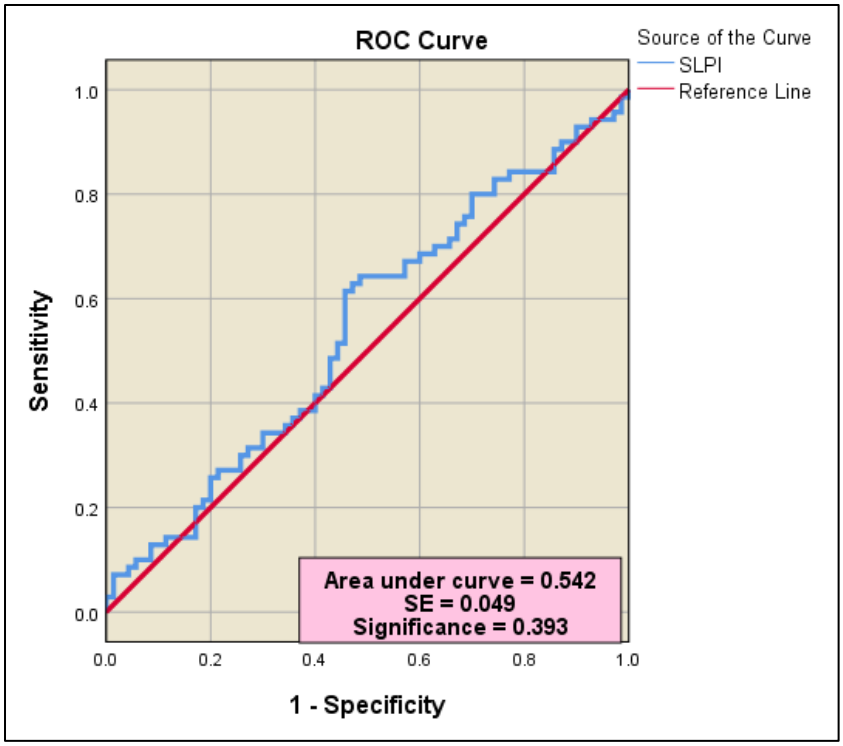


Figure (4.9): Receiver Operating Characteristic Curve and Area Under the ROC of SLPI Result (UTI Patients vs Asymptomatic Bacteriuria).

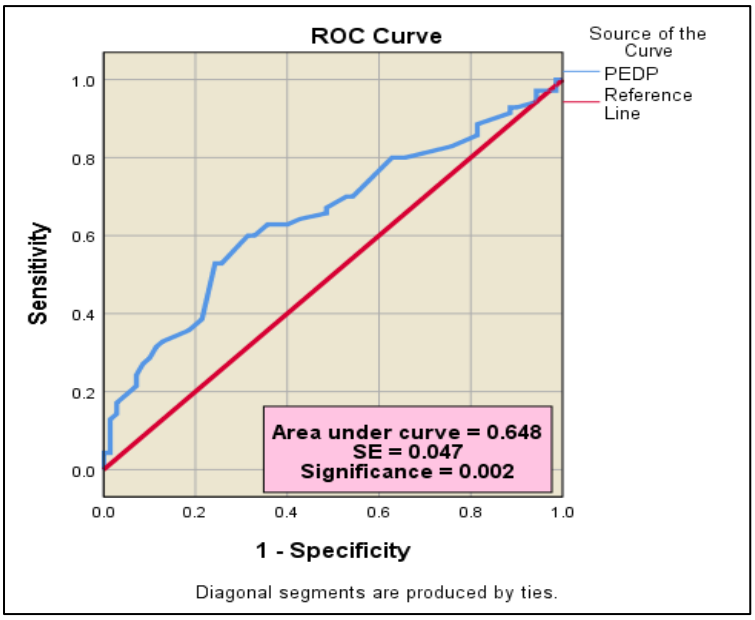


Figure (4.10): Receiver Operating Characteristic Curve and Area Under the ROC of PEDP Result (UTI Patients vs Asymptomatic Bacteriuria).

Table (4.19): ROC Analysis of Studied Variables

Variable	Area	Std. Error [a]	Asymptotic Sig. [b]	CI 95%	
				Lower Bound	Upper Bound
pH	0.737	0.042	0.000	0.654	0.820
RBC	0.632	0.047	0.007	0.540	0.724
Pus Cell	0.626	0.049	0.010	0.531	0.721
Epithelial Cell	0.518	0.049	0.706	0.422	0.614
PEDP	0.648	0.047	0.002	0.557	0.740
SLPI	0.542	0.49	0.393	0.446	0.638

b, Null hypothesis: true area = 0.5; a, Under the Nonparametric Assumption; CI, Confidence Interval; PEDP, Pus Epithelial Dual Presence.

Conclusions and Recommendations

Conclusions

The current study concludes the following:

1. A notable proportion of UTI patients had positive urine culture, while a considerable segment of the healthy control group was found to have ABU.
2. Significant lower percentage in the history of recurrent UTI was found in ABU in comparison to UTI patients.
3. *E. coli* and *S. saprophyticus* had the highest frequency among bacteria isolated from urine samples.
4. There was no significant difference in the mean level of serum SLPI between UTI patients and control group.
5. SLPI levels were higher in younger individuals, significantly higher in healthy females with reproductive menarche (but not in UTI patients), and significantly lower in overweight UTI patients compared to healthy females.
6. The presence of lower mean in patients with burning sensation reflects the importance of SLPI role in inhibiting the inflammation during infection.
7. The absence or low levels of SLPI highlight its critical role in the innate immune response and in protecting against bacterial infections, as well as its impact on increasing the host's susceptibility to infection.
8. Approximately of both patients and control group had culture negative and positive RUTI and SLPI in third quartile (Q3). This may reflect that either recurrent infection may cause increase level of SLPI that affect the bacteria and thus no bacterial growth is found in culture or due to the presence of continuous inflammatory response that requires increase level of SLPI.

Recommendation

This study recommends the following:

1. Investigate the best way and time to collect the urine sample for detection of different types of proteins secreted in urine like SLPI in urine and compare it with the blood.
2. Study the association of SLPI with the disease severity and complication of UTI.
3. Study the relationship or association of SLPI level with the level of inflammation mediators (like IL-1β, IL-6, IL-8, TNF-α).
4. Investigate the presence of SLPI polymorphism between UTI patients in comparison to healthy control group.
5. Future studies should aim to encompass a broader range of patient populations—including children, pregnant women, and individuals with complicated UTIs or pyelonephritis—to determine whether SLPI exhibits similar diagnostic behavior across various clinical settings.

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Appendix

Appendix 1: Questionnaire

(Patient information form)

Patient name:

Number of samples:

Age of patient:

Address habitation:

Phone number:

Is there a possibility you may be pregnant	Yes		No	
Disease onset for	diabetes	asthma	cardiovascular disease	chronic kidney disease
	COVID-19	autoimmune disease	cancer	nephrolithiasis
Do you have a urinary catheter	Yes		No	
Have you had a recurrent Urinary tract infection (UTI) last	2 months	3 months	6 months	
Have you had any symptoms	Burning	Urgency	Frequency of urination	pain
Using any Antibiotics	Yes		No	
Educational state	student	An employee	None	
Marital status	Single		Married	
Menstrual period	Yes		No	
Time of Menstrual period	First day	Second day	>three days	
The menarche status	Reproductive period		Postmenopausal	

Hand wash after toilet	Yes			No		
Using toilet paper	Yes			No		
Hygienic product	Yes			No		
Wear cotton undergarment	Yes			No		
Washing undergarment	By hand			With machine		
Bath frequency	Every day			>2 per week		
Urination	continence			incontinence		
Weight (Kg)						
Height (m)						
Hypertension	Yes			No		
Smoker	Yes			No		
Tests to be done						
1-General urine examination (GUE)						
Macroscopic examination	Color	Appearance	PH	Specific gravity	Protein	Glucose
Microscopic examination	RBC		Pus cell		Epithelial cell	Cast
	Crystals		Amorphous		Bacteria	Others
2-Urine culture	Culture yielded			Isolated organism		
3- Measure Secretory leukocyte Protease Inhibitor						

Appendix 2: Human secretory leukocyte protease inhibitor ELISA Kit.

BT LAB
Bioassay Technology Laboratory

Optimize Your Research

USER INSTRUCTION

Cat.No E0850Hu

Standard Curve Range: 20-4500ng/L

Sensitivity: 10.23ng/L

Size: 96 wells / 48 wells

Storage: Store the reagents at 2-8°C. For over 6-month storage refer to the expiration date keep it at -20°C. Avoid repeated thaw cycles. If individual reagents are opened it is recommended that the kit be used within 1 month.

***This product is for research use only, not for use in diagnosis procedures. It's highly recommended to read this instruction entirely before use.**

Precision

Intra-Assay Precision (Precision within an assay) Three samples of known concentration were tested on one plate to assess intra-assay precision.

Inter-Assay Precision (Precision between assays) Three samples of known concentration were tested in separate assays to assess inter-assay precision.

CV(%) = SD/mean x 100

Intra-Assay: CV<8%

Inter-Assay: CV<10%

Intended Use

This sandwich kit is for the accurate quantitative detection of Human secretory leukocyte protease inhibitor (also known as SLPI) in serum, plasma, cell culture supernates, Ascites, tissue homogenates or other biological fluids.

Assay Principle

This kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The plate has been pre-coated with Human SLPI antibody. SLPI present in the sample is added and binds to antibodies coated on the wells. And then biotinylated Human SLPI Antibody is added and binds to SLPI in the sample.

Appendix 3: VITEK 2 System

Identification Information	Analysis Time:	5.78 hours	Status:	Final
Selected Organism	98% Probability	Klebsiella pneumoniae ssp pneumoniae		
	Bionumber:	6607734553165210		
ID Analysis Messages				

Susceptibility Information	Analysis Time: 9.20 hours			Status: Final	
Antimicrobial	MIC	Interpretation	Antimicrobial	MIC	Interpretation
ESBL	NEG	*+	Imipenem	0.5	S
Ampicillin	>= 32	R	Meropenem	<= 0.25	S
Amoxicillin/Clavulanic Acid	>= 32	R	Amikacin	>= 64	R
Piperacillin/Tazobactam	>= 128	R	Gentamicin	8	I
Cefalotin	>= 64	R	Ciprofloxacin	>= 4	R
Cefoxitin	>= 64	R	Tigecycline	2	S
Ceftazidime	>= 64	R	Nitrofurantoin	256	R
Ceftriaxone	>= 64	R	Trimethoprim/Sulfamethoxazole	>= 320	R
Cefepime	>= 64	R			

+= Deduced drug *= AES modified **= User modified

AES Findings	
Confidence:	Consistent with correction

Appendix 4: Approval Letter

University of Kerbala
College of Applied Medical Sciences
Ethics Committee

July :01/2025
Reference No: CLAMSKU/8

To: Saja Hadi Abdul Hamza E-mail: saja.hadi@s.uokerbala.edu.iq
Proposal Title: Evaluation of Secretory Leukocyte Protease Inhibitor in Diagnosis of UTI in Female

Approval Letter

Dear Saja Hadi Abdul Hamza

Your application to carry out the study proposal and the documents below in the Department of Clinical Laboratories was recently examined and considered by the College of Applied Medical Sciences study Ethics Committee.

1. The proposal description
2. Consent form

The research proposal is authorized to proceed in its current form by the College of Applied Medical Sciences Ethical Committee. Not a single investigator or co-investigator involved in the study participated in the voting or decision-making process.

The College of Applied Medical Sciences Ethics Committee requests a copy of the final report and expects to be updated on the study's progress, along with any significant adverse events that may occur, protocol revisions, and patient information and informed consent.

The College of Applied Medical Sciences' biomedical research rules are followed by this ethics committee.

Prof. Dr. Hadi Rasool Hassan	Prof. Dr. Hassan Ali Hussein	Dr. Karrar Sadeq Khudhair
The Chair	Member	Member

الخلاصة

تعد التهابات المسالك البولية (UTIs) مشكلة متزايدة الاهمية في مجال الصحة العامة على مستوى العالم, لما تسببه من تكاليف صحية كبيرة وتؤثر سلبًا على جودة حياة المرضى في جميع أنحاء العالم. وبناءً على ذلك، تتزايد الحاجة إلى تطوير مؤشرات حيوية أكثر موثوقية لتحسين تشخيص حالات التهاب المسالك البولية.

يعد مثبط بروتياز الكريات البيضاء الافرازي (SLPI) من مثبطات السيرين بروتياز، ويمتاز بخصائصه المضادة للالتهابات والبكتيريا. وقد تم توثيق الدور المهم لهذا المثبط خلال حالات (UTI), الا أن أهميته كمؤشر حيوي محتمل لتشخيص تلك الحالات لا تزال بحاجة إلى مزيد من الدراسة .

تم اعتماد تصميم دراسة حالة-شاهد، حيث شملت الدراسة 140 امرأة تتراوح أعمارهن بين 18 إلى 58 سنة، وجرى تقسيمهن إلى مجموعتين: 70 مريضة مصابة بالتهاب المسالك البولية، و70 امرأة يتمتعن بصحة جيدة كمجموعة ضابطة. وتمت مطابقة المجموعتين من حيث العمر ومكان الإقامة. جُمعت عينات البول والدم في الفترة الممتدة من سبتمبر 2024 إلى ديسمبر 2024 في العيادة الاستشارية للمسالك البولية في مستشفى الإمام الحسين، في مدينة كربلاء المقدسة. استُخدمت عينات البول في الفحص العام للبول والزراعة البكتيرية، بينما استُخدمت عينات الدم لقياس مستويات (SLPI) باستخدام تقنية ELISA.

لوحظ متوسط العمر في المجموعتين (39.36±14.28) و(39.10±14.38) سنة على التوالي. وُجد أن الفئة العمرية 18-37 سنة سجلت النسبة الأعلى من التكرار في كل من مرضى UTI والمجموعة الضابطة. وبالنسبة إلى حالة البلوغ، كانت 50 (71.4%) من المريضات و58 (82.9%) من النساء السليمات في مرحلة الإنجاب. أما بالنسبة لمؤشر كتلة الجسم(BMI) ، فقد بلغ متوسطه في مجموعات مريضات UTI (26.99±0.75 و30.09±0.89)، وفي المجموعات الضابطة (30.40±1.34 و28.57±0.87).

كانت حوالي 59 (84.3%) من مريضات UTI لديهن عدوى متكررة(rUTI) ، بينما كانت النسبة 26 (37.1%) في المجموعة الضابطة. أظهر الفحص العام للبول فروقاً ذات دلالة إحصائية بين المجموعتين من حيث وجود الخلايا القيحية. وبالنسبة لنمو البكتيريا في زراعة البول، وُجدت نتائج إيجابية لدى 40 (57.1%) من المريضات و28 (40.0%) من المجموعة الضابطة. وكانت الإشريكية القولونية (*E.coli*) البكتيريا الأكثر شيوعاً لدى مريضات UTI (52.5%) وفي حالات البيلة الجرثومية اللاعرضية (ABU) (46.4%), تلتها المكورات العنقودية الصفراوية (*S. saprophyticus*) بنسبة (32.5% و32.1%) ، ثم المكورات العنقودية البشروية (*S. epidermidis*) بنسبة (10.0% و14.3%) على التوالي.

لم تُسجّل فروق ذات دلالة إحصائية في مستويات SLPI في الدم بين المجموعتين. إلا أن مستويات SLPI كانت أعلى لدى النساء السليمات في الفئة العمرية 18–37 ولدى من يعانين من زيادة الوزن. كما كانت المستويات أعلى بصورة ملحوظة لدى النساء السليمات في مرحلة الإنجاب.

لوحظ فيما يخص البيانات السريرية للمريضات، ارتفاع متوسط SLPI لدى من يعانين منrUTI ، والإلحاح البولي، وعدم وجود ألم فوق العانة، والتبول المنتظم، وغياب ارتفاع ضغط الدم، وعدم استخدام المضادات الحيوية. وبناءً على نتائج شريط الفحص السريع ، وُجدت فروق ذات دلالة إحصائية في مستويات SLPI بين المجموعتين حسب فئات الرقم الهيدروجيني ، وداخل مجموعة الضابطة أيضاً. لم تكن هناك فروق ذات دلالة إحصائية ($P > 0.05$) في متوسط مستوى SLPI بين المجموعات المدروسة حسب نتائج فحص البول العام .

الجدير بالذكر أن أعلى متوسط لمستويات SLPI سُجل لدى المريضات المصابات بـ*S. epidermidis* ، وفي حالات ABU مع وجود*E.coli*. كان متوسط SLPI أعلى بشكل ملحوظ لدى المجموعة الضابطة السليمة ($P = 0.014$)مقارنةً بمرضى UTI الذين أظهروا أربعة نتائج اختبار إيجابية (أي كان لديهم ارتفاع في مؤشرات مثل درجة الحموضة، خلايا القيح(النسبة الطبيعية اقل من 5 خلايا/ HPF)، كريات الدم الحمراء (النسبة الطبيعية من 2-3 خلية/ HPF)، الخلايا الطلائية، ملاحظة وجود البكتيريا تحت المجهر). حوالي 25 (58.1%) من المرضى والأصحاء كانت نتائجهم سلبية في الزرع البكتيري، ولكن كانت لديهم حالات التهاب متكرر (RUTI) ومستوى SLPI في الربع الثالث .(Q3) وقد يعكس ذلك أن العدوى المتكررة قد تؤدي إلى زيادة مستوى SLPI مما قد يؤثر على البكتيريا ويثبط نموها في الزرع، أو قد يعكس وجود استجابة التهابية مستمرة تتطلب ارتفاع مستوى SLPI.

أظهرت نتائج الدراسة أن المساحة تحت المنحنى (AUC) للمتغيرات التاليةpH :، والخلايا القيحية، وخلايا الدم الحمراء، وPEDP، وSLPI، والخلايا الطلائية كانت (0.737)، (0.626)، (0.632)، (0.648)، (0.542)، و(0.518) على التوالي. ما يدل على أن SLPI يمتلك قدرة تمييزية منخفضة للكشف عنUTI ، بينما كان لقيمة pH أعلى قدرة على التمييز بين المرضى والأصحاء.

أظهرت النتائج أن (57.1%) من مريضات UTI كانت لديهن نتائج إيجابية في زراعة البول، مقابل (40%) من المجموعة الضابطة واللواتي يعانين من .ABU وكانت هناك فروق ذات دلالة إحصائية في تاريخ العدوى المتكررة (rUTI) بين المجموعتين، حيث كانت النسبة أعلى لدى المريضات. لم تختلف خصائص لون

ومظهر البول بين المريضات والمجموعة الضابطة، ما قد يعكس عدم فائدة هذه المعايير في تشخيصUTI ، في حين قد يكون لعكارة البول أهمية تشخيصية. وكانت *E. coli* و *S. saprophyticus*أكثر البكتيريا شيوعاً في عينات البول.

لم تختلف مستويات SLPI في الدم بين المريضات والمجموعة الضابطة، ما قد يعكس عدم تأثر SLPI في حالات UTI السفلية ما لم تتطور العدوى إلى إصابة جهازية أو التهابات الكلى (pyelonephritis). من جهة أخرى، قد يشير غياب SLPI أو انخفاض مستوياته إلى أهميته في المناعة الفطرية والدفاع ضد العدوى البكتيرية وزيادة القابلية للإصابة. وُجد أن متوسط SLPI أعلى لدى الفئات العمرية الأصغر. ولم تُظهر النتائج أي ارتباط معنوي بين مستويات SLPI ومعلمات تحليل البول. وامتلكت قيمة pH أعلى قدرة تمييزية بين المرضى والأصحاء، تلتها خلايا الدم الحمراء والخلايا القيحية، بينما أظهر SLPI قدرة تنبؤية ضعيفة. وكان لمؤشر PEDP قيمة AUC أعلى من الخلايا القيحية وحدها.

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة كربلاء

كلية العلوم الطبية التطبيقية

قسم التحليلات المرضية

تقييم مثبطات بروتياز الكريات البيضاء الإفرازية كعلامة حيوية في تشخيص التهاب المسالك البولية في النساء

رسالة مقدمة

الى مجلس كلية العلوم الطبية الطبيقية - جامعة كربلاء

وهي جزء من متطلبات نيل شهادة الماجستير في التحليلات المرضية

كتبت بواسطة

سجى هادي عبدالحمزة

بكالوريوس تحليالت مرضية / كلية العلوم الطبية التطبيقية / جامعة كربلاء, 2019

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