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Molecular Detection of *UreC* and *mrpA* Genes in *Proteus mirabilis* Isolated from Kidney Stone Patients

Böbrek Taşı Hastalarından İzole Edilen *Proteus mirabilis*'teki *ureC* ve *mrpA* Genlerinin Moleküler Yöntemlerle Tespiti

Fatima Amer Abd Algabar[1], Athmar Adnan Hakman[2], Ahmed Dawood Ahmed[3]

[1]*Middle Technical University, College Baquba, Department Medical Laboratory Technique, Baquba, Iraq*
[2]*University of Diyala, College of Science, Department of Biotechonolgy, Diyala, Iraq*
[3]*Bilad Al-Rafidain University, College of Medical Technologies, Department Medical Laboratory Techniques, Diyala, Iraq*

Abstract

Introduction: Nephrolithiasis is one of the most common chronic kidney disorders in patients with hypertension. This study aimed to identify and isolate *Proteus mirabilis* from the urine samples of kidney stone patients, investigate the presence of the *ureC* and *mrpA* genes using polymerase chain reaction (PCR), and assess the levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and CCL2 in these patients.

Materials and Methods: Fifty urine samples were obtained from the Urology Department of Baghdad Teaching Hospital in Baghdad Governorate between March 2025 and the end of November 2025. Twenty healthy individuals participated in this study as controls. Blood samples were acquired from the patients and controls to assess their TNF-α, IL-6, and CCL2 levels.

Results: The results of the present study indicated that *Proteus mirabilis* was the most abundant bacterium, as identified in 10 (20%) cases, followed by *Escherichia coli* and *Staphylococcus aureus*, each present in seven instances (14%). *Pseudomonas aeruginosa* was identified in six (12%) cases, while *Klebsiella pneumoniae* was detected in five (10%) cases. Molecular approaches using PCR to target the *ureC* and *mrpA* genes yielded results indicating that the *ureC* gene was present in 70% of the samples, while *mrpA* was detected in 60% of the samples. Furthermore, these findings indicated elevated levels of TNF-α, IL-6, and CCL2 in kidney stone patients.

Conclusion: It was revealed that *Proteus mirabilis* was the predominant bacterium in patients with renal stones and that it possesses the *ureC* and *mrpA* genes, which contribute to the pathogenicity of bacteria. This study also showed that TNF-α, IL-6, and CCL2 tend to increase in kidney stone patients.

Keywords: IL-6, kidney stone, *mrpA*, *Proteus mirabilis*, TNF-α, *ureC*, virulence genes

Öz

Giriş: Nefrolitiyazis, hipertansiyonu olan hastalarda en sık görülen kronik böbrek hastalıklarından biridir. Bu çalışma, böbrek taşı hastalarının idrar örneklerinden *Proteus mirabilis*'i izole edip tanımlamayı, polimeraz zincir reaksiyonu (PCR) kullanarak *ureC* ve *mrpA* genlerinin varlığını araştırmayı ve bu hastalardaki TNF-α, IL-6 ve CCL2 düzeylerini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Mart 2025 ile Kasım 2025 sonu arasında Bağdat Valiliği'ndeki Bağdat Eğitim Hastanesi Üroloji bölümünden 50 idrar örneği alınmıştır. Ayrıca, çalışmaya kontrol grubu olarak 20 sağlıklı birey dahil edilmiştir. TNF-α, IL-6 ve CCL2 düzeylerinin incelenmesi amacıyla hastalardan ve kontrol grubundan kan örnekleri alınmıştır.

Bulgular: Çalışma sonuçları, en sık görülen bakterinin *Proteus mirabilis* olduğunu (10 olguda, %20) ve bunu her biri 7 olguda (%14) tespit edilen *Escherichia coli* ile *Staphylococcus aureus*'un izlediğini göstermiştir. *Pseudomonas aeruginosa* 6 olguda (%12), *Klebsiella pneumoniae* ise 5 olguda (%10) tespit edilmiştir. *ureC* ve *mrpA* genlerini hedef alan PCR tabanlı moleküler analizler, örneklerin %70'inde *ureC*, %60'ında ise *mrpA* geninin bulunduğunu ortaya koymuştur. Mevcut araştırma, böbrek taşı hastalarında TNF-α, IL-6 ve CCL2 düzeylerinin arttığını göstermiştir.

Address for Correspondence/Yazışma Adresi: Fatima Amer Abd Algabar, MD, Baqubah Technical College, Middle Technical University, Diyala, Iraq
E-mail: fatmaamer@mtu.edu.iq **ORCID ID:** orcid.org/0000-0003-4181-2163
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Sonuç: Bu araştırma, böbrek taşı olan hastalarda baskın bakterinin *Proteus mirabilis* olduğunu ortaya koymuştur. Sonuçlar, *Proteus mirabilis*'in bakterinin patojenitesine katkıda bulunan *ureC* ve *mrpA* genlerini taşıdığını göstermektedir. Ayrıca çalışma, böbrek taşı hastalarında TNF-α, IL-6 ve CCL2 düzeylerinde artış olduğunu ortaya koymuştur.

Anahtar Kelimeler: IL-6, böbrek taşı, *mrpA*, *Proteus mirabilis*, TNF-α, *ureC*, virülans genleri

Introduction

Renal stones, also known as urolithiasis and kidney stones, are solid aggregates that form in the kidneys from dissolved urinary minerals[1]. These stones can cause severe pain, hematuria, and complications, such as urinary tract infections (UTIs) and kidney disease. The lifetime risk of developing kidney stones is approximately 12% for men and 7% for women, with recurrence rates up to 50% within 5–10 years after the first episode. Many risk factors have been proven to precipitate renal stones, including genetic, dietary, and environmental factors[2,3].

Although kidney stones smaller than 5 mm flow readily through the urinary tract, those larger than 5 mm can precipitate, resulting in calculus development[4]. The most prevalent types of stones are calcium oxalate and calcium phosphate, constituting at least 80% of all kidney stones. The remaining urinary stones consist of uric acid, cysteine, and mixed forms. The acute edges of oxalate calculi tend to injure the urinary tract epithelium and promote the proliferation of organisms by creating a nidus for infectious agents[5,6].

The prevalent and misguided application of antibiotics has contributed to the issues associated with UTIs[7]. The rise of antibiotic resistance constitutes a significant challenge for the medical community and poses a substantial threat to public health[8]. Urease-producing bacteria, including *Proteus mirabilis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, are consistently associated with the formation and recurrence of struvite stones[9]. The pathogenicity of *Proteus mirabilis* is influenced by a variety of virulence genes that promote adhesion, colonization, immune evasion, and tissue damage, advancing the infectious process in diverse host conditions[10,11]. *ureC* and *mrpA* are unique virulence genes associated with the pathogenicity of *Proteus mirabilis*[12,13]. The *ureC* gene encodes the alpha subunit of urease, which promotes the formation of bladder and kidney stones by catalyzing the hydrolysis of urea[14]. The ureolytic activity of *Proteus mirabilis* generates ammonia and carbonate ions, increasing the urine pH[15] and precipitating calcium and magnesium phosphates. Microcrystals become ensnared in biofilms, resulting in the development of crystalline biofilms that can encrust and obstruct urinary catheters. Obstructed catheters can cause urine retention in the bladder and retrograde flow to the kidneys, resulting in recurrent UTIs. Failure to replace obstructed catheters may result in pyelonephritis, septicemia, and endotoxic shock[16].

Chemokines are low-molecular-weight proteins whose principal function is to direct the migration of immune cells to specific target areas. CCL2, or monocyte chemoattractant protein-1 (MCP-1), is considered a crucial regulatory element in inflammatory responses. Consistent with previous observations, renal tubular epithelial cells can synthesize CCL2 in response to calcium oxalate stimulation[17-19]. Interleukin-6 (IL-6) is a multifunctional cytokine that modulates immunological responses and is regarded as an endogenous pyrogen that induces fever in infected individuals. Following infection and inflammation, IL-6 is initially produced, with its levels swiftly increasing to a peak within 2 hours[20].

Tumor necrosis factor-alpha (TNF-α) is a macrophage-derived endogenous modulator of several host responses to infection and inflammation[21]. Several studies have reported that renal stones may induce renal cells to release inflammatory mediators in vitro, including MCP-1 (often referred to as CCL2), TNF-α, and IL-6. Consequently, the inflammatory responses of renal tissue significantly contribute to the pathogenesis of urolithiasis[22].

Although the association between *Proteus mirabilis* and UTIs and the formation of infectious kidney stones has been well established, published data on the molecular distribution of certain virulence-related genes among the isolates of this bacterium from kidney stone patients, particularly in Iraq, have been limited. Thus, further research on these two genes may contribute to a deeper understanding of the virulence characteristics of these bacteria and their potential contribution to infection and stone formation.

Materials and Methods

Fifty urine samples were obtained from the Urology Department of Baghdad Teaching Hospital in Baghdad Governorate between March 2025 and the end of November 2025. Their ages ranged from 35 to 64 years, encompassing both sexes.

Sample Collection

During sample collection, the initial urine drops were disregarded, and the midstream urine was collected and stored in sterile containers. Subsequently, it was sent to the Postgraduate Microbiology Laboratory at the College of

Science, Department of Biology, for culture and diagnostic purposes. Moreover, 5 mL of venous blood was drawn from each specimen using a sterile disposable syringe and permitted to coagulate at ambient temperature. The tubes underwent centrifugation at 3000 rpm for a duration of 15 minutes. Subsequently, the tubes were stored at a temperature of -20 °C until the assay, which encompassed the following parameters: TNF-α, IL-6, and CCL2.

Inclusion and Exclusion Criteria

This study included only those patients for whom the attending urologist diagnosed kidney stones on the basis of clinical examination and imaging (ultrasonography or computed tomography) findings. Only adult patients (35–64 years old) who had not been exposed to any antibiotic treatment in the preceding 2 weeks before sampling were included. The exclusion criteria were patients with chronic inflammatory disease, autoimmune disorders, malignancies, severe renal failure, or any other systemic infection. The control group comprised apparently healthy subjects with no history of kidney stones or UTIs.

Isolation and Identification

The diagnosis was made based on[16] the morphological characteristics, such as growth on blood agar, MacConkey agar, and mannitol salt agar. Moreover, microscopic examination and biochemical tests were performed. The identification results were subsequently confirmed using the VITEK 2 automated identification system.

DNA Extraction and Molecular Detection of the *ureC* and *mrpA* Genes

Proteus mirabilis was cultivated in brain heart infusion broth and incubated for 24 hours at a temperature of 37 °C. In accordance with the manufacturer's instructions, genomic DNA was extracted using the FavorPrep Blood/Cultured Cell Genomic DNA Extraction Mini Kit. To ensure the sample quality for downstream molecular investigations, the extracted DNA concentration and purity were assessed using the Quantus™ Fluorometer. Table 1 shows the primers used to detect *Proteus mirabilis* and its virulence gene using polymerase chain reaction (PCR): The initial denaturation was 1 cycle at a temperature of 94°C for 3 min, followed by 35 cycles of 40 seconds each of denaturation at 94 °C, annealing at 60 °C, and elongation at 72 °C. The reaction was finished with 1 cycle of 72°C elongation for 7 minutes. The samples were electrophoresed on a 1.5% agarose gel to validate the reaction and create predicted bands.

Table 1. The primers used in this investigation.

Gene	Sequence	Product size	Reference
ureC	5′-CCGGAACAGAAGTTGTCGCTG GA-3′	533 bp	[16]
	5′-GGGCTCTCCTACCGACTTGATC-3′		
mrpA	5′-TTCTTACTGATAAGACATTG-3′	410 bp	[16]
	5′-ATTTCAGGAAACAAAAGATG-3′		

Evaluation of TNF-α, IL-6, and CCL2

All study samples were measured using enzyme-linked immunosorbent assay (Elabscience®, Wuhan, China) in accordance with the manufacturer's instructions.

Ethical Approval

This study was conducted on urine samples collected as part of routine laboratory investigations, with no direct patient intervention. Thus, formal ethical approval was not required according to the institutional guidelines. All procedures were performed in accordance with relevant regulations and ethical standards.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). Data were expressed as mean ± standard deviation. The normality of the data was established using the Shapiro-Wilk test. For the normally distributed continuous variables, the independent samples t-test was used, whereas for the categorical variables, the chi-square test or Fisher's exact test may be used, depending on the circumstances. Furthermore, statistical significance was set at a p value of <0.05.

Results

A total of 50 urine samples were analyzed. Bacterial growth was detected in 35 (70%) samples, whereas 15 (30%) samples showed no bacterial growth. Among the positive cultures, *Proteus mirabilis* was found to be the most common bacterium in 10 isolates (20%), followed by *Escherichia coli* and *Staphylococcus aureus* (7 isolates each; 14%), *Pseudomonas aeruginosa* in 6 isolates (12%), and *Klebsiella pneumoniae* in 5 isolates (10%) (Table 2).

Table 2. Frequency of bacterial isolates in the kidney stone patients.

Type of bacteria	Number of isolates	Percentage (%)
Proteus mirabilis	10	20%
Escherichia coli	7	14%
Staphylococcus aureus	7	14%
Pseudomonas aeruginosa	6	12%
Klebsiella pneumoniae	5	10%
No bacterial growth	15	30%
Total	50	100%

Differential media were used to distinguish *Proteus mirabilis* from other Enterobacteriaceae: the bacterial isolates on blood agar showed swarming and hemolysis, whereas on MacConkey agar, they were non-lactose fermenters and had pale, round, convex, smooth colonies with a fish-like odor (Figures 1 and 2). The biochemical test was used to describe the *Proteus mirabilis* isolates. All 10 isolates tested positive for catalase, citrate, and urease but negative for indole and oxidase (Table 3).

The findings of the present investigation suggest that seven (70%) of the *Proteus mirabilis* isolates had the *ureC* gene detected by amplifying bacterial DNA using the PCR method at 533 bp, whereas three isolates (30%) were negative (Figure 3). Moreover, six (60%) of the *Proteus mirabilis* isolates had the *mrpA* gene detected by amplifying the bacterial DNA for this gene using the PCR method at 410 bp, while four isolates (40%) did not carry this gene, as shown in Figure 4.

In the present study, the mean serum level of IL-6 in the kidney stone patients was 7.62 ± 11.5 ng/mL, while the mean serum level of the control group was 5.05 ± 4.9 ng/mL, as shown in Figure 5. This result was highly significant ($p = 0.002$). The mean serum levels of TNF-α and CCL2 in the present study among the kidney stone patients were 18.61 ± 0.21 ng/mL and 211 ± 19.21 ng/mL, respectively, compared with 3.46 ± 0.13 ng/mL and 76.4 ± 5.3 ng/mL in the controls. These differences were also deemed statistically significant ($p = 0.001$), as shown in Figures 6 and 7, respectively.



Figure 1. *Proteus mirabilis* on MacConkey agar.



Figure 2. *Proteus mirabilis on blood agar.*

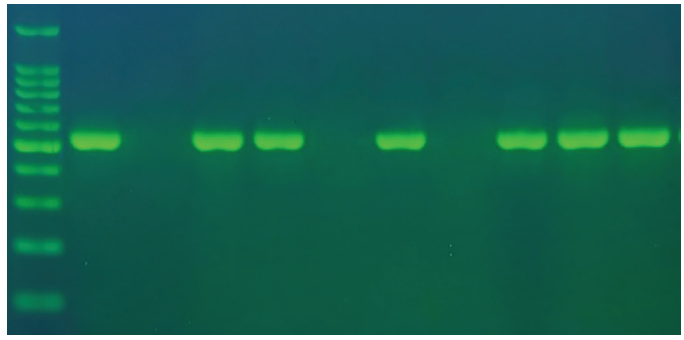


Figure 3. The polymerase chain reaction product exhibits a band size of 533 base pairs. The sample was subjected to electrophoresis on 1.5% agarose using 1 TBE buffer for 1 hour and 30 minutes. N: DNA ladder (100 base pairs).

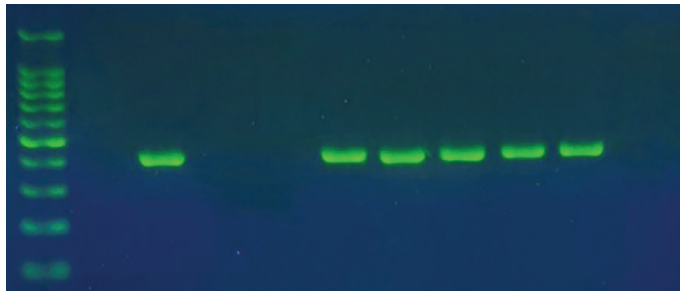


Figure 4. The polymerase chain reaction result shows a band size of 410 base pairs. The sample was subjected to electrophoresis on 1.5% agarose using 1 TBE buffer for 1 hour and 30 minutes. N: DNA ladder (100 base pairs).

Table 3. Biochemical test for *Proteus mirabilis*

Catalase	Oxidase	Citrate	Indole	Urease	MR/VP	TSI
+	-	+	-	+	-/+	H_2S+

R, methyl red; VP, Voges–Proskauer; TSI, triple sugar iron; H_2S, hydrogen sulfide.

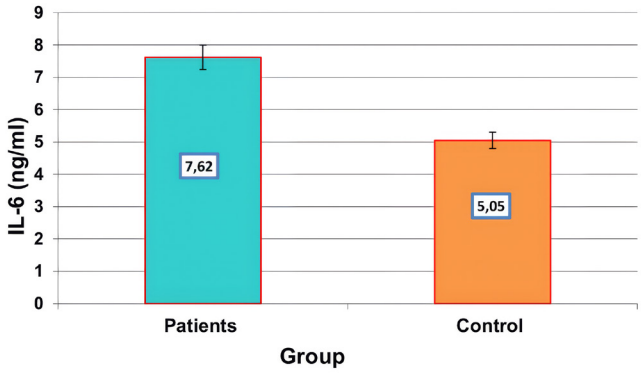


Figure 5. Mean level of IL-6 (ng/mL) in the kidney stone patients and controls. IL-6, interleukin-6.

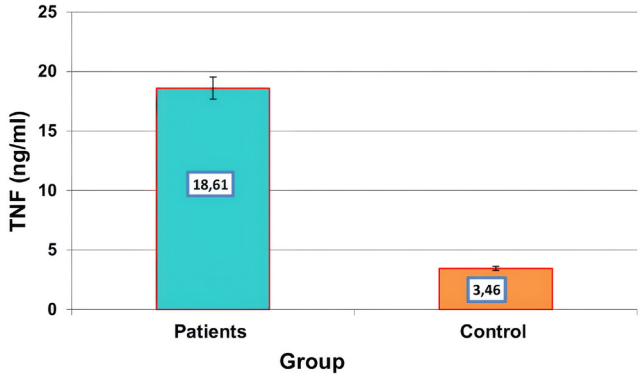


Figure 6. Mean level of TNF-α (ng/mL) in the kidney stone patients and controls. TNF-α, tumor necrosis factor-alpha.

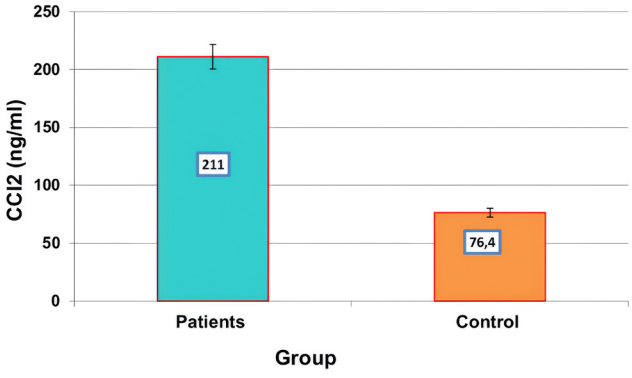


Figure 7. Mean level of CCL2 (ng/mL) in the kidney stone patients and controls.

Discussion

Until recently, it was suggested that only urease-producing bacteria were involved in the pathophysiology of urolithiasis and the formation of struvite stones. Researchers believe that bacteria might help make all kinds of stones, even non-struvite stones. This is because struvite stones are not as common as the other types of stones and people with urolithiasis are more likely to get UTIs and positive urine cultures[23]. The findings of the present study showed that *Proteus mirabilis* was the predominant bacterium, followed by *Escherichia coli* and *Staphylococcus aureus*.

The present study is consistent with previous studies conducted by[24], which reported that the percentage of isolated *Proteus mirabilis* was 19.04%, and with the study conducted by[25], which indicated that *Proteus mirabilis* is the most abundant organism in patients with kidney stones. Another study[26] showed a correlation between renal stones and *Escherichia coli*, *Enterococci*, *Micrococcus luteus*, and *Staphylococci* spp. This result contradicts that of the study conducted by[27], which indicated that *Staphylococcus* spp. was the predominant genus in the stones and urine of patients with kidney stones. The formation of these outcomes can be attributed to multiple factors, including environmental conditions, host characteristics, and microbial interactions[28]. Antibiotic usage, hospitalization, and host immunological condition may affect the predominance of specific bacterial species. Furthermore, the transmission dynamics of these bacteria in healthcare environments or communities may influence their differing prevalence rates[29]. *Proteus mirabilis* possesses several virulence genes associated with infection. The results reveal that the prevalence rate of *ureC* genes was seven (70%) and that of *mrpA* genes was six (60%). Urease (*ureC*) is a virulence gene crucial to the pathogenesis of *Proteus mirabilis*. This enzyme facilitates the formation of kidney stones. It is also crucial for urolithiasis, as it hydrolyzes urea to release ammonia, hence increasing urine pH, which results in the precipitation of calcium and magnesium compounds and the production of kidney stones[12]. The presence of these genes may contribute to the pathogenicity and virulence of the bacterial strains[17]. The *mrpA* gene, for instance, has been related with certain features, such as adhesion, biofilm formation, and resistance to host defenses[18]. The findings of the present study are consistent with those of a previous study[30] that revealed detection rates of the *mrpA* gene of 75% but contradict with the findings of[16],

which reported a 100% detection rate. The *mrpA* gene encodes a mannose-resistant *Proteus*-like fimbriae component needed for urinary tract bacterial adhesion, colonization, and biofilm formation. These fimbriae help bacteria settle in the urinary system and weaken the immune system, prolonging infection. MRPA may increase virulence, which may affect the treatment outcomes by increasing bacterial resistance to human defenses and antimicrobials[31].

The present study indicated an increase in the TNF-α, IL-6, and CCL2 levels in the kidney stone patients compared with the controls. The results are consistent with those of[32-34] indicating increased levels of TNF-α, IL-6, and CCL2. This may result from inflammatory responses induced by the kidney stones, perhaps leading to other urinary system infections. TNF-α is associated with various renal pathologies, and its association with clinical factors has been documented in chronic kidney disease[35]. Ahuja et al.[36] reported that circulating IL-6 drives inflammatory responses through CXCL1 synthesis following acute renal damage in mice. The results indicated that the plasma levels of TNF-α were downregulated, while the plasma concentrations of IL-6 were increased in patients following percutaneous nephrolithotripsy relative to the preoperative values[37]. Boonla et al.[38] showed an increased mRNA expression of IL-6 and MCP-1 in renal biopsy tissue from the kidneys with calculi. The role of IL-6 in stone formation, whether it is released due to the mechanical stimulation of epithelial cells or contributes to renal stone development, remains ambiguous[39,40].

Study Limitations

This study has several limitations that should be addressed. The sample size was relatively limited, and the samples were obtained from a single center, which may affect the generalizability of the findings. The cross-sectional nature of the study does not allow the establishment of causal relationships. However, the use of both microbiological and molecular techniques, along with the evaluation of key inflammatory biomarkers (TNF-α, IL-6, and CCL2), provides valuable insights into the studied condition. Thus, further studies with larger sample sizes and multicenter designs are recommended to further validate these findings.

Conclusion

The present study showed that *Proteus mirabilis* was the most prevalent bacterium in kidney stone patients. The results indicated that *Proteus mirabilis* carries the *ureC* and *mrpA* genes, which contribute to the pathogenicity of bacteria. Furthermore, this study also suggested that TNF-α, IL-6, and CCL2 tend to increase in kidney stone patients.

Ethics

Ethics Committee Approval: This study was conducted on urine samples collected as part of routine laboratory investigations, with no direct patient intervention. Thus, formal ethical approval was not required according to the institutional guidelines. All procedures were performed in accordance with relevant regulations and ethical standards.

Informed Consent: As the study was conducted using urine samples collected during routine laboratory investigations, without direct patient intervention, the requirement for informed consent was waived in accordance with institutional guidelines.

Footnotes

Authorship Contributions

Concept: F.A.A.A., A.D.A., Design: A.A.H., Data Collection or Processing: F.A.A.A., A.A.H., A.D.A., Analysis or Interpretation: F.A.A.A., A.A.H., Literature Search: A.A.H., A.D.A., Writing: F.A.A.A., A.D.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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