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The relationship between TLR4 gene polymorphism (rs7873784, G/C) and urinary tract infections caused by multidrug-resistant bacteria among Iraqi patients

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***Abstract*— Toll-Like Receptor 4 (TLR4) is a pattern recognition receptor (PRR) that identifies pathogen-associated molecular patterns (PAMPs) molecules found on the surface of bacteria, viruses, and other pathogens. This study aimed to evaluate the relationship between functional gene polymorphisms (*TLR4*-rs7873784) and susceptibility to multidrug-resistant (MDR) bacteria in urinary tract infections (UTIs). A total of 350 urine samples were collected from males and females aged 10–75 years at Al-Rifae General Hospital in Thi-Qar province, southern Iraq, between July 2022 and January 2023. All bacterial isolates were identified biochemically and by VITEK-2 system then confirmed with 16SrRNA gene. Resistance genes were detected using bacterial colonies in a PCR test. Tetra-ARMS-PCR was used to detect TLR4 gene polymorphism (rs7873784).150 samples (42.9%) showed positive bacterial growth, while 200 samples (57.1%) were culture-negative. The samples that were positive for bacterial growth were 150 samples, including 30 XDR samples, 20 sensitive to antibiotics, and 100 MDR samples, pathogens isolated MDR included *Escherichia coli* (44%), *Staphylococcus aureus* (33%), *Klebsiella pneumoniae* (10%), and *Proteus mirabilis* (13%). Regarding resistance genes: BlaCTX-M was detected in 81.8% of *E. coli*, 100% of *K. pneumoniae*, and 30.8% of *P. mirabilis*; BlaSHV in 29.5% of *E. coli*, and 100% of both *K. pneumoniae* and *P. mirabilis*; BlaAMPC in 90.9% of *E. coli*, 100% of *K. pneumonia*, and 30.8% of *P. mirabilis*; and BlaTEM in all Gram-negative isolates. Additionally, the mecA, ermA, and ermC genes were found in 100% of S. aureus isolates. Analysis of TLR4 SNPs revealed that the homozygous CC and heterozygous GC genotypes of TLR4-rs7873784 was significant risk factor indicating increased susceptibility to MDR UTIs in individuals carrying these genotypes.**

***Keywords*—Gene polymorphism, Multiple drug resistance, TLR4, UTI**

I. INTRODUCTION

Urinary tract infection (UTI) is an infection that occurs in any part of the urinary system, including the urethra, bladder, ureters, and kidneys. UTI was classified as either uncomplicated infections such as cystitis and pyelonephritis in people without any structural or neurological abnormalities of the urinary tract or complicated urinary tract infection include factors that weaken the urinary tract or the body's defenses, urinary obstruction, urinary retention, immunodeficiency, kidney failure, pregnancy, and the presence of an indwelling catheter or other drainage device [1]. There are various causes of urinary tract infections, often determined by several factors such as time, patient age, and immunity. The most common bacteria causing UTIs are *Escherichia coli*, *Klebsiella* and *Proteus* pp, with differences in the order of frequency among patients [2].

Multidrug resistance (MDR) refers to the situation in which a microorganism exhibits resistance to at least one antimicrobial agent in three or more different classes of antimicrobials [3]. Infections caused by multidrug-resistant microorganisms constitute a major global problem due to their economic and clinical burden. Therefore, considerable importance has been given to addressing this growing issue [4]. Multidrug -resistant bacteria have become an increasingly common cause of urinary tract infections in both community-acquired and healthcare-associated cases, potentially resulting in higher treatment failure rates [5]. The excessive and inappropriate use of antibiotics without performing antimicrobial susceptibility testing has led to the emergence of UTI-causing bacteria resistant to multiple antibiotics [6].

Toll-like receptors are a set of pattern recognition receptors that play a central role in identifying pathogen-associated molecular patterns through the innate immune response TLRs achieve their role by inducing antimicrobial activity and generating inflammatory cytokines. Moreover, they are vital for tissue repair and regeneration [7].Tetra-ARMS-PCR has been applied to identify the single nucleotide polymorphism (SNP) [8] it extricates the individual DNA mutation is homozygous or heterozygous [9].

The selection of the TLR4 gene polymorphism rs7873784 (G/C) in the present study was based on several scientific criteria. First, previous evidence has indicated that rs7873784 is located within a regulatory region of the TLR4 gene, suggesting that it may influence gene expression and downstream inflammatory pathways [10]. Second, this SNP

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has been reported to be associated with susceptibility to chronic periodontitis in Asian populations, highlighting its potential functional relevance in immune-mediated diseases [10]. Third, additional studies have demonstrated links between rs7873784 and respiratory conditions such as chronic obstructive pulmonary disease and pulmonary tuberculosis, supporting its broader role in modulating innate immune responses [11]. Based on this collective evidence, rs7873784 was selected as a biologically meaningful and clinically relevant candidate SNP for evaluation in our population.

The present study aimed to evaluate the association between functional polymorphisms TLR4TLR4-rs11536889 and susceptibility to develop multidrug-resistant bacteria in urinary tract infections by the following objectives:

1. Association between TLR4 gene polymorphism and urinary tract infections caused by multidrug-resistant bacteria in Iraqi patients in the southern regions.
2. Detection of TLR4 receptor gene polymorphism *TLR4*-rs7873784 G/C in whole Blood Sample of patient with UTI and healthy control by Amplification Refractory Mutation System polymerase chain reactions (ARMS-PCR).

II. METHOD

a) The study design.

The current study was designed as a case-control study. A total of 350 urine samples were collected from male and female patients with a mean age of 34.09 ± 18 years (range: 10–75) between July 2022 and January 2023. For this purpose, face-to-face interviews were conducted with patients who applied to Al-Rifae General Hospital in Thi-Qar province in southern Iraq. During these interviews, patient age, gender, signs and symptoms, and whether or not they had received antibiotic treatment in the week prior to sample collection were recorded. Urinary tract infection (UTI) patients were diagnosed according to clinical and laboratory criteria. Clinical criteria were based on signs and symptoms, while laboratory criteria included general urine examination.

Among the patients, 100 individuals diagnosed with UTIs caused by multidrug-resistant bacteria were specifically included for further analysis, from whom blood samples were also collected. Additionally, 100 healthy individuals without UTIs were recruited as the control group. This precise selection allowed for a direct comparison between infected patients and healthy controls to investigate the genetic and clinical factors associated with UTI susceptibility and multidrug resistance

Microscopic analyses were performed for the presence of pus cells, bacteria, and positive urine culture containing <105 CFU/mL bacteria in the patient and control groups. Sterile screw-capped containers were used to collect midstream urine samples for definitive diagnosis of urinary tract infections. All samples were then inoculated onto Blood Agar, MacConkey Agar and A sterile standard ring (0.001 mL) was inoculated at 37°C for 24 h. Cell morphology of pure bacterial colonies was examined using Gram staining reagents. All bacterial isolates were identified biochemically and by VITEK-2 system. All isolates were then confirmed with 16SrRNA gene and resistance genes were detected using bacterial colonies in a PCR test.

3 mL blood sample was collected from patients with urinary tract infection (UTI) and healthy controls. Blood samples were preserved in tubes containing K3-EDTA and stored at 4°C until DNA was extracted and purified. Amplification refractory mutation system polymerase chain reaction (ARMS-PCR) was used to detect TLR4 gene polymorphism (rs7873784) in patient and healthy control blood samples the extracted total DNA was checked by using Nanodrop (Thermo Scientific NanoDrop Lite UV Visible Spectrophotometer. USA) that measured DNA concentration (ng/µL) and checked the DNA purity at absorbance (260 /280 nm). then PCR Master Mix Preparation and PCR Product Analysis

The PCR products were analyzed by agarose gel electrophoresis method as following steps:

1. 1.5% Agarose gel was prepared in using 0.5X TBE and dissolving in microwave for 5 minutes, and left to cool for 50°C.
2. Then 3µl ethidium bromide stain were added into agarose gel solution.
3. Agarose gel solution was poured in tray after fixed the comb in proper position and left to solidified for 15 minutes at room temperature, then the comb was removed gently from the tray.
4. The gel tray was fixed in electrophoresis chamber and filled by 0.5X TBE buffer.
5. 10µl PCR product were loaded in to each well with added 5µl (DNA marker Ladder) in first well. Then electric current was performed at 100 volt and 80 AM for 1 hour.
6. PCR products were visualized by using UV Transilluminator [12].

TABLE 1 PCR PRİMERS WİTH NUCLEOTİDE SEQUENCES AND PRODUCT SİZES

Primary		Sequence (5'-3')	Product size	Genbank ID number
16S rRNA gene Escherichia coli	F	TCCCCATCTTTGTCCATCTC	453bp	LR739012.1
	R	AGAATACCGGTGACGAATGC		
16S rRNA gene Staphylococcus aureus	F	GAGGGTCATTGGAAACTGGA	611bp	L37597.1
	R	TAGCACGTGTGTAGCCCAAA		
16S rRNA gene *Proteus mirabilis*	F	CAGAAGAAGCACCGGCTAAC	368bp	LR739004.1
	R	CGGTTTCAAGACCACCAACCT		
16S rRNA gene Klebsiella pneumoniae	F	ACCTTGGCGATTGACGTTAC	562bp	HG416956.1
	R	AAGGGCACCAATCCATCTCTG		

TABLE 2: PCR PRİMERS, NUCLEOTİDE SEQUENCES AND PRODUCT SİZES OF BETA-LACTAM ANTİBİOTİC RESİSTANCE GENES ASSOCİATED WİTH GRAM-NEGATİVE BACTERİA

Primary	Sequence (5'-3')		Product size	Genbank ID number
BlaCTX-M	F	CAGACTGGGTGTGG CATTGA	241 bp	OM32 6869.1
	R	GCTAAGCTCAGCCA GTGACA		
blaSHV	F	TATCGGCCCTCACT CAAGGA	412 bp	OL906 381.1
	R	ATCGCTCATGGTAA TGGCGG		
blaTEM	F	GAGAGTTTTCGCCC CGAAGA	522 bp	ON221 404.1
	R	AATAAACCAGCCAG CCGGAA		
blaAMPC	F	ACATCTCGCAACCT ACACCG	655 bp	LC455 576.1
	R	ATAGCTACCAAATC CGCCGG		

TABLE 3: PCR PRİMERS, NUCLEOTİDE SEQUENCES AND PRODUCT SİZES OF BETA-LACTAM ANTİBİOTİC RESİSTANCE GENES ASSOCİATED WİTH GRAM-POSİTİVE BACTERİA

Primary	Sequence (5'-3')		Product size	Genbank ID number
*Staphylococcus aureus*mecA	F	ACCTCTGCTCAACAA GTTCCA	683 bp	KC24 3783.1
	R	ACCACCCAATTTGTCT GCCA		
*Staphylococcus aureus*ErmA	F	AGCGGTAAACCCCTC TGAGA	306 bp	KT80 3896.1
	R	ACAGAGTCTACACTT GGCTTAGG		
*Staphylococcus aureus*ermC	F	TGGCTCAGGAAAAAG GGCATT	558 bp	JF968 539.1
	R	TCGTCAATTCCCGCAT GTTT		

b) Statistical analysis

Data were collected, summarized, analyzed and presented using statistical package for social sciences (SPSS) version 26 and Microsoft Office Excel 2010. Numeric data were presented as mean, standard deviation after performance of Kolmogorov- Smirnov normality test and making decision about normally and non-normally distributed variables. Independent sample t-test was used to study difference in mean between any two groups provided that the variable was normally distributed. One way was Anova test that was used to study difference in the mean between more than two groups provided that the variable was normally distributed. Chi-square test was used to study association between any two categorical variables. Odds ratio and 95% confidence interval was estimated to measure risk. The level of significance was considered at P-value of less 0.05 and highly significant level at 0.01 or less [10].

III. RESULTS

a) Bacterial Isolation from Urine Samples

The study included a total of 350 participants aged between 10 and 75 years, representing a wide range of age groups that may influence susceptibility to urinary tract infections. When urine samples were cultured, 150 individuals (42.9%) showed positive bacterial growth, indicating the presence of a urinary tract infection based on the culture criteria used in the study. The remaining 200 participants (57.1%) exhibited no bacterial growth, suggesting either the absence of infection, prior antibiotic exposure, or non-bacterial causes of urinary symptoms (Figure.1).

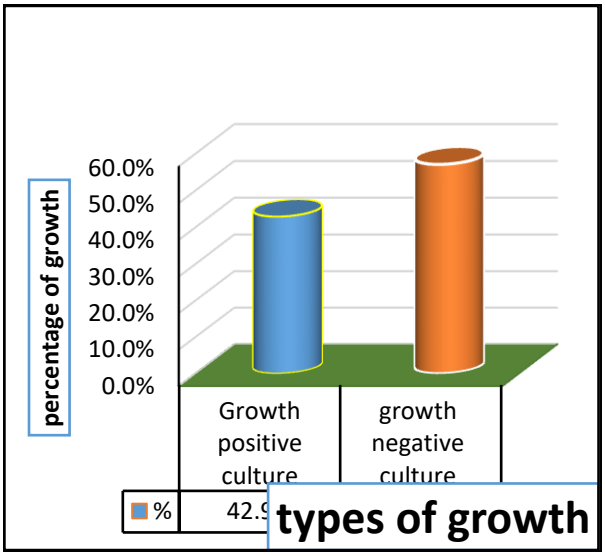

Figure1: Bacterial Isolation from Urine Samples

b) Types of drug resistance in bacterial samples

A total of 350 individuals, aged 10 to 75 years, participated in the study. Among these participants, 150 individuals (42.9%) exhibited positive bacterial growth in their urine cultures, indicating the presence of a urinary tract infection. In contrast, 200 individuals (57.1%) showed no bacterial growth, suggesting either the absence of infection or the possibility of non-bacterial causes. Among the 150 culture-positive samples, 100 isolates were classified as multidrug-resistant (MDR), demonstrating resistance to at least one agent in three or more antimicrobial categories. Additionally, 30 isolates were identified as extensively drug-resistant (XDR), showing resistance to nearly all tested antibiotic classes. The remaining 20 isolates were antibiotic-sensitive, displaying susceptibility to the antimicrobial agents used in the study.

TABLE 5 TYPES OF DRUG RESİSTANCE İN BACTERİAL SAMPLES

Bacterial samples	Sensitive	Multi-drug resistant (MDR)	Extensively Drug-Resistant (XDR)	pan drug Resistant (PDR)	*P*

Staphylococcus aureus	5 (%3,3)	33 (%22)	13 (%8,7)	0(%0)	
Escherichia coli	9 (%6)	44 (%29,3)	9 (%6)	0(%0)	0,635 ¥: NS
Klebsiella pneumonia	2 (%1,3)	10 (%6,7)	5 (%3,3)	0(%0)	
Proteus mirabilis	4 (%2,7)	13 (%8,7)	3 (%2)	0(%0)	
Total	20 (%13,3)	100 (%66,7)	30 (%20)	0(%0)	

n: number of cases; SD: standard deviation; ¥: Chi-square test; NS: significant at P <0.05.

c) Percentages of MDR bacteria according to PCR diagnosis of urinary tract infection

The current study included 350 urine samples, from which 100 multidrug-resistant (MDR) isolates were selected for further analysis. The PCR-based bacterial identification revealed the following distribution of uropathogens responsible for urinary tract infections: 44 isolates (44%) *Escherichia coli*, 33 isolates (33%) *Staphylococcus aureus*, 13 isolates (13%) *Proteus mirabilis*, and 10 isolates (10%) *Klebsiella pneumoniae*, as shown in Figure 2 .

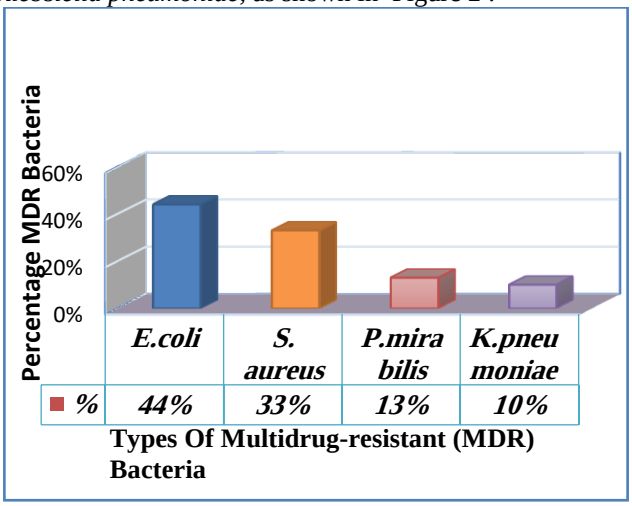

Figure 2: Percentages of MDR bacteria according to PCR diagnosis of urinary tract infection

Detection of mecA, ermA and ermC genes of Staph. Aureus Specific PCR primer was used for the molecular finding of *mecA, ermA and ermC genes* among *S. aureus* isolates. This study was found that all three genes (*mecA, ermA and ermC*) was observed in all *S. aureus* isolates, 33 (100.0%) as shown in table 6.

TABLE 6: DETECTION OF *MECA, ERMA AND ERMC GENES* OF *STAPH. AUREUS*

Results	Antibiotic resistance genes		
	mecA	*ErmA*	*ermC*
	Frequency	Frequency	Frequency
Positive, (%)	33 (100.0%)	33 (100.0%)	33 (100.0%)
Negative, (%)	0	0	0

d) Detection of blactx-m, blashv, blatem and blaampc genes in gram-negative bacterial species

Specific PCR primer was used for the molecular finding of BlaCTX-M, BlaSHV, BlaAMPC and BlaTEM genes among gram negative bacterial isolates This study was found that (*BlaCTX-M*) gene was observed in 36 (81.8%) of *E. coli isolates, all K. pneumonia* isolates 10 (100.0%) and only 4 (30.8%) of *P.mirabilis* i*solates*, and the difference was significant (P= 0.001), as shown in table (7),*BlaSHV* gene was observed in only 13 (29.5%) of *E.coli* isolates, but present in all *K. pneumonia* isolates 10 (100.0%) and *P. mirabilis* i*solates* 13 (100.0%), and the difference was significant (P= 0.001), and BlaTEM *gene* in all gram negative bacterial isolates while *BlaAMPC gene* was observed in 40 (90.9%) of *E. coli* isolates, all *K. pneumonia* isolates 10 (100.0%) and only 4 (30.8%) of *P. mirabilis* i*solates*, and the difference was significant (P= 0.001). as shown in table (7).

TABLE 7 DETECTION OF BLACTX-M, BLASHV, BLATEM AND BLAAMPC GENES IN GRAM-NEGATIVE BACTERIAL SPECIES

Antibiotic resistance genes	**Bacterial samples**			***p***
	E. coli	***K. pneumonia***	***P. mirabilis***	
BlaCTX-M gene				
Positive, n (%)	36 (81.8%)	10 (100.0%)	4 (30.8%)	0.001 ¥ S
Negative, n (%)	8 (18.2%)	0	9 (69.2%)	
BlaSHV gene				
Positive, n (%)	13 (29.5%)	10 (100.0%)	13 (100.0%)	0.001 ¥ S
Negative, n (%)	31 (70.5%)	0	0	
BlaTEM gene				
Positive, n (%)	44 (100.0%)	10 (100.0%)	13 (100.0%)	
Negative, n (%)	0	0	0	
BlaAMPC gene				
Positive, n (%)	40 (90.9%)	10 (100.0%)	4 (30.8%)	0.001 ¥ S
Negative, n (%)	4 (9.1%)	0	9 (69.2%)	

SD: standard deviation; n: number of cases; ¥: chi-square test; S: significant at p<0.05

e) Detection of TLR4-rs7873784 Polymorphism:

The TLR4-rs7873784 polymorphism was genotyped using the Amplification Refractory Mutation System–Polymerase Chain Reaction (ARMS-PCR), a method that relies on the specificity of allele-specific primers to distinguish between wild-type and mutant alleles. In this technique, two forward primers are designed: one specific for the G allele and one specific for the C allele, along with a common reverse primer. Each primer selectively amplifies only when its 3′-end nucleotides perfectly matches the target allele, allowing accurate discrimination of genotypes at this locus, three possible genotypes were detected. The wild-type homozygous genotype (GG) showed amplification of the G-specific fragment only, producing a band of 300 bp. The mutant homozygous genotype (CC) showed amplification of the C-specific fragment only, producing a band of 368 bp. In contrast, the heterozygous genotype (GC) exhibited amplification of both allele-specific fragments, resulting in the presence of both 300 bp (G-allele) and 368 bp (C-allele) bands; the combined band pattern confirmed the heterozygous state. This ARMS-PCR–based approach

allowed reliable and precise identification of the rs7873784 genotypes in all samples (Figure 3).

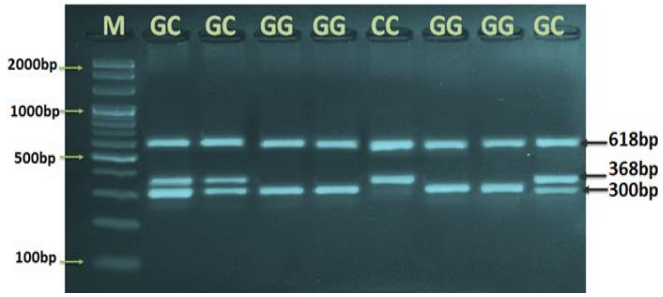

Figure 3 Fig. 3: Agarose gel electrophoresis image showing T-ARMS-PCR product analysis for TLR4 rs7873784 G/C gene polymorphism

f) Hardy Weinberg equation (TLR4-rs7873784)

Table 8 presents the results of applying the Hardy-Weinberg equation to the distribution of TLR4-rs7873784 genotypes (GG, GC, and CC) within the control group. The homozygous wild genotype GG was observed in 55 out of 100 control subjects The GC genotype (heterozygous) was observed in 30 out of 100 control subjects, while the CC genotype (homozygous mutant) was observed in 15 out of 100 control subjects. The distribution of control subjects based on TLR4-rs7873784 genotypes is significantly different from what was expected (P=0.017).

TABLE 8 HARDY WEINBERG EQUATION (TLR4-RS7873784)

	Observed	Expected	$\chi 2$	*P*
reference GG	55	49	8.163	0.017 ¥ S
GC	30	42		
variant CC	15	9		

g) Genotypic and allelic analysis for the studied gene in patients and healthy controls

Table 9 presents the comparison of genotype and allele frequencies of TLR4-rs7873784 SNP between patients and healthy controls. Concerning the co-dominant mode, the frequency distribution of genotypes shows a significant difference between patient and control groups (P=0.001). The risk analysis showed that the homozygous CC genotype was a considerable risk factor (OR=2.9). Moreover, the heterozygous GC genotype significantly increased risk (OR=4.35). Thus, individuals with the homozygous CC genotype had about three times the likelihood of developing the disease in comparison to those with other genotypes. Upon reviewing the dominant mode analysis, a notable difference was identified between the patient and control groups (p>0.05). In the context of allele analysis, there was also a significant difference observed between the patient and control groups (P=0.001). As for the recessive mode, though, the difference between patients and control groups was not significant (p>0.05. In genetic association studies, three primary inheritance models were applied to evaluate the relationship between genetic variants and disease risk. In the co-dominant model, each genotype (GG, GC, CC) was analyzed separately, assuming that the heterozygous genotype (GC) exerted an effect that is distinct from both homozygous genotypes. In the dominant model, individuals carrying at least one copy of the minor or risk allele (GC + CC) grouped together and compared with those carrying the GG genotype, based on the assumption that a single copy of the allele was sufficient to influence the phenotype. In contrast, the recessive model considers individuals with two copies of the minor allele (CC) as the at-risk group and compares them with the combined GG + GC group, since the phenotypic effect appears only when both allele copies are present. These genetic models offer complementary frameworks for understanding how the G and C alleles contribute to disease susceptibility [13].

TABLE 9 TLR4-RS7873784 POLY GENOTYPE FREQUENCY İN PATİENTS AND HEALTHY CONTROLS

Mode	TLR4-rs7873784	Sick *n*=100	Control *n*=100	*P*	OR	95% CI
Co-dominant Model	CC	19 (19.0%)	15 (15.0%)	0.001 ¥ S	2.9	1.2-6.65
	G/C	57 (57.0%)	30 (30.0%)		4.35	2.26-8.35
	GG	24 (24.0%)	55 (55.0%)		Reference	
Dominant Model	CC+G/C	76 (76.0%)	45 (45.0%)	0.001 ¥ S	Reference	
	GG	24 (24.0%)	55 (55.0%)		0.258	0.14-0.47
Recessive Model	CC	19 (19.0%)	15 (15.0%)	0.451 ¥ NS	1.32	0.63-2.79
	G/C+GG	81 (81.0%)	85 (85.0%)		Reference	
Alle	C	95 (47.5%)	60 (30.0%)	0.001 ¥ S	2.11	1.4-3.18
	G	105 (52.5%)	140 (70.0%)		Reference	

¥: Chi-square test; NS: Not significant at P>0.05 level; S: Significant at P≤0.05 level

Frequency distribution of genotype according to bacterial species

The frequency distribution of genotype according to species of bacteria was showed in tables 10. The present results showed there was significant association between bacterial species and results of ARMS-PCR (p = 0.017).

TABLE10 COMPARİSON OF GENOTYPE FREQUENCY DİSTRİBUTİON ACCORDİNG TO BACTERİAL SPECİES

Characteristic	*E. coli*	*K. pneumoniae*	*P. mirabilis*	
Genotype				
GG, n (%)	11 (25.0%)	0	4 (30.8%)	0.017 ¥ S
GC, n (%)	28 (63.6%)	6 (60.0%)	3 (23.1%)	
CC, n (%)	5 (11.4%)	4 (40.0%)	6 (46.1%)	

SD: standard deviation; n: number of cases; ¥: chi-square test; S: significant at $p<0.05$

IV. Discussion

A total of 350 people, aged between 10 and 75, participated in the study. 150 (42.9%) of these samples had positive bacterial growth and 200 (57.1%) had negative bacterial growth in urine samples. The present results are consistent with the study conducted by [14] in northwestern Ethiopia on 384 patients, 61 (15.9%) of 384 urine samples were positive and 323 (84.1%) were negative. In addition, in another study conducted by [15] in which 320 urine samples were examined, 50 (15.6%) samples were positive and 270 (84.4%) samples were negative. the results of the study conducted by [16] in Thi-Qar province, Iraq, where 150 urine samples were examined, showed positive bacterial growth in 87 samples (58%) and negative bacterial growth in 63 (42%) samples.

These results obtained in the studies do not agree with the results obtained in our study. In some samples, no growth was observed in the culture medium. This may be due to the presence of sterile pyuria or urinary tract stones. In addition, the agreements and disagreements between our study and other studies may be due to different environmental conditions and practices such as different geographical regions, differences in the recognition of UTI, screening methods and confounding risk factors, socioeconomic standards, education programs, health care and hygiene practices. The increase in antibiotic resistant bacteria is due to the increasing irrational use of antibiotics, easy availability of antimicrobials in unregulated pharmacies, transfer of resistance genes among humans and overprescribing. All these are factors that increase the growth of resistance and excessive bacterial resistance in the general population. This leads to overuse of high potency antibiotics for UTIs, which increases bacterial resistance. Antimicrobial resistance among uropathogens has increased alarmingly through different resistance mechanisms. S. aureus has developed resistance mechanisms against most antibiotics used against it through penicillin binding protein-2a (PBP2a), penicillinase, ribosomal methylation of binding sites and modification of efflux pumps. Similar to all β-lactam drugs, S. aureus has also acquired methicillin resistance through the evolution of PBP2a, which is resistant to all β-lactam antibiotics [17].

In our study, *E. coli* bacteria ranked first with 44 samples (44%). This result was consistent with the results of the study was done by [18],[19], [15] but it is not consistent with the results of the study was conducted by [20]. The normal flora of the intestine includes *E. coli.* Infection typically arises from hand contamination, the anatomical characteristics of women, and the closeness of the urethral area to the rectum. All of these factors can lead to an ascending infection to the bladder, resulting in cystitis and acute nephritis when it reaches the kidney. The presence of potent virulence factors, particularly enzymes and adhesion factors that aid in circumventing the host's mechanical defenses, heightens the severity of its pathogenicity. This can result in acute infections and inflammatory responses that may contribute to the onset of UTIs [21].

In the current study, it was registered 100% positive mecA which agrees with [22]. This resistance to Staphylococcus aureus attributed to the presence of the mecA gene, located in the SCCmec mobile gene the mecA gene encodes the PBP20 (PBP2a) gene, responsible for methicillin resistance and cross-resistance to other beta-lactam drugs [23].The resistance of *S. aureus* to erythromycin antibiotic returned to a common mechanism that confers resistance to the entire macrolide group. Methyltransferase enzymes are very important in this process, and these enzymes are encoded by three genes well-known as the erm genes [24].

The current result is consistent with the findings [25] in China which examined 130 *E. coli* isolates from hospitals in different Chinese towns. The blaCTX-M gene was amplified in 126 isolates (96.9%) of the ESBL-producing isolates. Our results are also consistent with those of [26] who isolated 99 samples of *Klebsiella pneumonia* These results are also consistent with those of [27] in Tanzania, where 98.9% of E. coli isolates were found to contain ESBL genes (such as blaCTX-M, blaTEM, or blaSHV) while only 1% were negative. Furthermore, these results are consistent with those reported by [28] which showed that only 1% of isolates were negative for the tested ESBL genes, while the blaampC gene was detected in 80% of clinical isolates in contrast. Our results are inconsistent with those of [29] in Benin City, Nigeria, which showed that 29.7% of 350 samples contained uropathogenic *E. coli* they also conflict with the results of [30] in Dhi Qar Governorate, Iraq, which indicated that 90 (14.3%) of 630 samples taken from pregnant women were Gram-negative.the high prevalence of ESBL enzymes in this study may be attributed to the uncontrolled use of antibiotics and their over-the-counter sale in Iraq as well as the lack of interest in routine laboratory testing for ESBL production in clinical isolates [31].

The Single-nucleotide polymorphism (SNP) examined in this study is rs7873784. This SNP, the nucleic acid G is the major allele at this locus, with the potential for conversion into multiple nucleic acid forms (A, C, or T). According to the TOPMED frequency estimator, the alternative C allele of this SNP is present at a frequency of 0.164846 the Qatar population exhibits a relatively lower frequency for this SNP at 0.116. However, the lowest recorded frequency for this SNP is found in the Japanese population at 0.084. Interestingly, our study has revealed that the minor allele C is present in 0.475 among the investigated Iraqi patients the reason for this higher frequency may be linked to various technical and non-technical factors associated with the distribution patterns of the rs7873784 SNP within the studied population. One technical explanation for these noticeable differences may be attributed to the limited sample size used in the current investigation due to this technical limitation, the results obtained may have been influenced by the specific individuals selected for the study [32].

Moreover, the accuracy of the genotyping and data analysis methods employed in this study could also contribute to these findings. Potential errors or biases in the processes of data collection and analysis may result in inflated allele frequencies alternatively, and it's possible that the population under investigation descended from a small

number of founders with a specific genetic makeup. This could lead to the preservation and even enrichment of particular genetic variants, including the minor allele in question Iraq exhibits substantial genetic diversity, and there may be subpopulations with unique genetic profiles. The UTI patients studied might belong to a subpopulation with a higher frequency of the minor allele. Conversely, we observed a significant difference in the genotype frequency distribution between the UTI patients and the control group ($p = 0.001$). This disparity suggests a significant divergence in the genetic composition of the patients compared to the control group under this mode subsequent risk analysis provided further insights into the relationship between genotypes and disease susceptibility

The homozygous CC genotype was identified as a significant risk factor, with an odds ratio (OR of 2.9) indicating that individuals with this genotype are nearly three times more likely to develop the disease compared to individuals with other genotypes. Aldditionally, individuals with the heterozygous G/C genotype were identified as a significant risk factor with an OR of 4.35, underscoring its role in increasing disease susceptibility. The findings from our analysis of the dominant mode indicated a significant difference between the patients and the control group, implying that the presence of the dominant allele may contribute to the disease. However, the exact significance level (p-value) was greater than 0.05, suggesting that this mode may not be as strongly associated with disease susceptibility as the co-dominant mode in our allele analysis. We identified a significant difference between the patients and the control group ($P = 0.001$), signifying that the specific alleles in question play a role in the risk of developing UTI. This finding underscores the importance of considering individual alleles when evaluating genetic susceptibility to the disease on the other hand, our analysis of the recessive mode did not reveal a significant difference between the patients and the control group ($p > 0.05$). This implies that the presence of two copies of the recessive allele does not substantially affect disease susceptibility. However, it's crucial to note that non-significance in this mode does not rule out the possibility of an association, as the sample size and other factors can influence the statistical outcome. The mode of action of this SNP has recently been demonstrated by [33].

In the context of our study focusing on the polymorphism of the rs7873784 SNP in UTI patients, it's noteworthy that there's a remarkable lack of relevant information in the existing literature. This specific genetic variation might play a pivotal role in urinary tract infections has received relatively limited attention. The conspicuous absence of literature in this area underscores the importance of our investigation. Urinary tract infections are a prevalent medical concern with significant implications for public health [34] The interaction of genetic factors in the susceptibility, progression, and treatment response of UTIs is an increasingly researched topic [35]. Nonetheless, there is a noticeable research gap concerning rs7873784 and its polymorphism in UTI patients. Our study contributes to filling this knowledge void by offering one of the initial insights into the potential link between rs7873784 polymorphism and UTIs. By scrutinizing this specific genetic variant, we aimed to uncover potential associations that could enhance our comprehension of UTI etiology. Our research has employed rigorous methodology and data analysis to investigate this relationship. However, the scarcity of available research on the association between the rs7873784 SNP and UTI has led us to explore the role of this SNP in other diseases and metabolic syndromes.

Consequently, the investigated rs7873784 SNP has demonstrated variable contributions across a wide range of diseases, including cancer, diabetes mellitus, rheumatoid arthritis, and various other pathological conditions. The minor C allele of the rs7873784 SNP has demonstrated its relevance in various medical conditions. Notably, it has been linked to an increased risk of rheumatoid arthritis in the Chinese population [36]. Additionally, this SNP has shown associations with a broad spectrum of pathologies characterized by chronic inflammation [37]. Furthermore, combined meta-analyses have confirmed significant associations between the rs7873784 polymorphism and tuberculosis in various ethnic populations [38] that reported differences in the frequencies of the GG genotype of rs7873784 between the control group and the acute respiratory distress syndrome group, with notably higher frequencies in the control group (P=0.000).

Interestingly, the concentration of serum TRL4 in patients with the CC (P=0.034) and CT (P=0.000) genotypes in the acute respiratory distress syndrome group was higher than that in the control group, shedding light on the possible role of this SNP in this condition. Furthermore, studies have explored the impact of rs7873784 on mental health [39]. They found that TLR4 influenced by the rs7873784-G allele, and played a significant role in anxiety, suicide, and other symptoms in patients with major depressive disorder, as evidenced by higher anxiety scores. Moving beyond mental health, an association between rs7873784 and higher odds of periodontitis in the Chilean population was revealed [40]. Another study also highlighted a significant link between homozygosity for the minor C allele of rs7873784 and the progression of prostate cancer [41]. Logistic analysis showed that rs7873784 was associated with risk of type-2 diabetes mellitus complicated by tuberculosis in additive and dominant models carriers with homozygous and heterozygous mutants of rs7873784 that had a higher risk than those with wild-type homozygotes, with an odds ratio of 1.61 [42]. Additionally, various studies have reported inverse associations between rs7873784 and the progression of prostate cancer [43]. This suggests that this SNP may exert a protective effect against the progression of prostate cancer in certain populations. Moreover, one study found that rs7873784 significantly protected against colorectal cancer, with an odds ratio of 0.71 [44]. The current results also showed a non-significant association between SNP rs7873784 and age groups, gender and residence ($P < 0.05$). *TLR-4* gene polymorphisms may be associated with susceptibility to UTIs, but this relationship can vary across populations and disease types [45].

We observed a prevalence of *E. coli* growth over other bacterial infections in the context of the currently investigated rs11536889 SNP. This prevalence of bacterial infections, particularly *E. coli*, has been consistent across all genetic forms of both SNPs *E. coli* is a natural resident of the human gastrointestinal tract, with a significant presence in the colon and rectum. This proximity to the urinary tract

creates an accessible route for *E. coli* to enter and infect the urinary system, making it a bacterium that is consistently in close proximity [46]. *E. coli* has developed specific adhesive structures, like fimbriae or pili, which enable it to attach to the urothelial cells lining the urinary tract. This adhesion represents a crucial initial step in the establishment of infection and gives *E. coli* an advantage over other bacteria that may lack similarly efficient adhesion mechanisms [47]. Another notable characteristic of *E. coli* is its higher capability to form biofilms, complex bacterial communities encased in a protective matrix. These biofilms can adhere to the bladder or urethral lining, essentially providing a safe haven for bacteria, making it challenging for both the immune system and antibiotics to clear the infection. The formation of biofilms is a unique strategy observed in specific E. coli strains [48].

In conclusion, our study has not only shed light on a previously uninvestigated genetic factor in UTIs but has also underscored the importance of genetic diversity in disease risk. These findings mark an important milestone in the ongoing quest to unravel the genetic complexities of UTIs and may pave the way for more effective diagnostics and interventions in the future. While the literature is currently lacking regarding the polymorphism of rs7873784 in UTI patients, our research takes a significant step toward filling this void. Our findings may inspire and facilitate future research endeavors in this area, ultimately advancing our understanding of urinary tract infections and their genetic underpinnings.

V. CONCLUSIONS:

Comparison of the genotypes and allele distribution of the TLR4-rs7873784 gene variant between patients and healthy controls, using a co-dominant inheritance model, revealed a statistically significant difference in the distribution of genotypes between the two groups ($p = 0.001$). The results of the risk factor analysis showed that the homozygous CC genotype (OR = 2.9) and the heterozygous GC genotype (OR = 4.35) represented statistically significant risk factors. These results indicate that individuals carrying the homozygous CC genotype are approximately three times more likely to develop disease than individuals carrying other genotypes.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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