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Prevalence of fluoroquinolone resistance genes in the *Escherichia coli* sequence type 131 clone isolated from hospitalized patients with urinary tract infection

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Abstract

Background: The emergence of fluoroquinolone (FQ) resistance in the *Escherichia coli* (*E. coli*) sequence type 131 (ST131) clone has become a major challenge in the management of urinary tract infections (UTIs). Chromosomal mutations and plasmid-mediated quinolone resistance (PMQR) determinants play an important role in FQ resistance.

Methods: This cross-sectional study was conducted in 2020 on 300 urine samples. It aimed to investigate the prevalence of chromosomal mutations, PMQR genes, including *qnr* and *aac* (*6′*)-*Ib-cr*, and efflux pumps among FQ-resistant ST131 and non-ST131 *E. coli* causing UTIs. Initially, the ST131 clone was detected using allele-specific PCR and confirmed by Multilocus Sequence Typing.

Results: Among 95 FQ-resistant *E. coli* isolates, 29 (30%) belonged to the ST131 clone. The most frequently detected PMQR genes in FQ-resistant isolates were *aac* (*6′*)-*Ib-cr* and *qnrS*. However, statistical analysis revealed a stronger association between *aac* (*6′*)-*Ib-cr* and the ST131 clone (62%; $p < 0.03$). The *oqxA* gene was the most prevalent efflux pump gene observed in both ST131 (n = 11; 38%) and non-ST131 (n = 16; 24%) isolates. Analysis of the *gyrA* and *parC* genes revealed a significantly higher frequency of mutations in ST131 compared with non-ST131. Double mutations, S80I + E84V, were significantly more prevalent in both *gyrA* (76% ST131 vs. 43% non-ST131; $p = 0.004$) and *parC* (55% ST131 vs. 26% non-ST131; $p = 0.002$). Notably, the substitution E84G was exclusive to non-ST131 isolates (n = 4). High-level resistance (MIC ≥ 32 µg/mL) was observed in 96.6% (28/29) of ST131 isolates compared with 65% (43/66) of non-ST131 isolates.

Conclusion: The double mutations confer high-level resistance to FQs in the ST131 clone. These findings regarding resistance mechanisms can guide infection control strategies.

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Introduction

Fluoroquinolones (FQs), such as ciprofloxacin (CIP) and levofloxacin (LEV), are broad-spectrum antimicrobials used to treat a wide range of hospital- and community-acquired infections, such as urinary tract infections (UTIs) (1,2). The extensive use of antibiotics, particularly FQs, has inadvertently driven the selection and proliferation of multidrug-resistant (MDR) strains, such as *Escherichia coli* (*E. coli*) sequence type 131 (ST131). ST131, a pandemic clone linked to the spread of extended-spectrum beta-lactamases (ESBLs), has emerged as a global threat to public health (3). ST131 exhibits multidrug resistance to a broad spectrum of antibiotics, including aminoglycosides, cephalosporins, and FQs. ST131 is the most common MDR high-risk clone in UTIs worldwide. The emergence and spread of the MDR *E. coli* ST131 clone, particularly isolates resistant to FQs, are a major concern worldwide (4,5). Chromosomal mutations in the quinolone resistance-determining regions (QRDRs) of DNA gyrase and topoisomerase IV-enzymes necessary for bacterial DNA replication and repair-are key mechanisms of quinolone resistance, including resistance to nalidixic acid and reduced susceptibility to FQs. These mutations can enable bacteria to produce enzymes that destroy FQs or prevent them from entering bacterial cells (6,7). Plasmid-mediated quinolone resistance (PMQR) is another common mechanism contributing to quinolone and FQ resistance among gram-negative bacilli. Based on their mechanisms, PMQR determinants are categorized into three classes, including various *qnr* alleles, such as *qnrA*, *qnrB*, and *qnrS*; efflux pump genes, such as *qepA* and *oqxAB*; and a variant of aminoglycoside acetyltransferase, *aac* (*6′*)-*Ib-cr* (8-10). FQ-resistant bacteria can use efflux pumps to transport FQs out of their cells. The aim of this study was to detect the ST131 clone among FQ-resistant *E. coli* isolates from patients with UTIs. Additionally, mutations in the DNA gyrase and topoisomerase IV genes, as well as the presence of PMQR and efflux pump genes, were investigated using polymerase chain reaction (PCR) in FQ-resistant *E. coli* isolates.

Methods

Bacterial isolates

A total of 250 *E. coli* isolates were obtained from the urine of hospitalized patients with UTIs in hospital wards in Tehran, Iran, in 2020. Standard bacteriological methods were employed to identify these *E. coli* isolates (11). Before participation in the study, each patient or their parent/guardian provided written informed consent and received an explanation regarding the study purpose.

Susceptibility of the *E. coli* isolates to FQs

The Kirby-Bauer disk diffusion technique was employed to determine the susceptibility of the *E. coli* isolates to antibiotic disks (MAST, England), including nalidixic acid (NAL; 30 µg) and ciprofloxacin (CIP; 5 µg), according to the CLSI guidelines (12). Then, the minimum inhibitory concentration (MIC) of CIP was determined by E-test. The CLSI breakpoints for CIP were susceptible at ≤ 1 µg/mL and resistant at ≥ 4 µg/mL. *E. coli* ATCC 25922 and *K. pneumoniae* were used as quality control strains.

DNA extraction

Genomic DNA of *E. coli* isolates from pure cultures were extracted using the boiling method and stored at -20°C until use. The quality of the extracted DNA was confirmed by NanoDrop (Thermo Scientific, Roskilde, Denmark). An absorbance ratio at 260/280 nm above 1.7 indicated acceptable purity (13).

Screening of the ST131 clone

After DNA extraction from *E. coli* isolates, the ST131 clone was screened through ST131-specific sequence polymorphisms in *mdh* and *gyrB* (14). The O25b-ST131 variant was detected using allele-specific PCR targeting the *pabB* gene (4). The *trpA* gene was amplified as an internal control for the PCR reactions (15). The Multilocus Sequence Typing (MLST) system was employed to confirm the ST131 clone using seven housekeeping genes, including *adk*, *fumC*, *gyrB*, *icd*, *mdh*, *purA*, and *recA* (http://enterobase.warwick.ac.uk/species/ecoli/allele_st_search). Table 1 lists the sequences of the primers used in this study.

Table 1. Primers used to detect the ST131 clone and fluoroquinolone resistance genes

Target gene	Primer	Sequence (5´- 3´)	Amplicon size (bp)	Annealing temp (°C)	References
pabB	O25pab-Bspe.F	TCCAGCAGGTGCTGGATCGT	347	63	(4)
	O25pab-Bspe.R	GCGAAATTTTTCGCCGTACTGT			
trpA	TrpA1.F	GCTACGAATCTCTGTTTGCC	427	63	(15)
	TrpA1.R	GCAACGCGGCCTGGCGGAAG			
rfbO25b	gndbis.F	ATACCGACGACGCCGATCTG	300	60	(41)
	rfbO25b.R	TGCTATTCATTATGCGCAGC			
qnrA	QnrA.F	AGAGGATTTCTCACGCCAGG	619	57	(17)
	QnrA.R	GCAGCACTATKACTCCCAAGG			
qnrB	QnrB.F	GGMATHGAAATTCGCCACTG	264	57	(17)
	QnrB.R	TTTGCYGYYCGCCAGTCGAA			
qnrS	QnrS.F	GCAAGTTCATTGAACAGGCT	428	57	(17)
	QnrS.R	TCTAAACCGTCGAGTTCGGCG			
qnrC	QnrC.F	GGGTTGTACATTTATTGAATC	447	58	(20)
	QnrC.R	TCCACTTTACGAGGTTCT			
qnrD	QnrD.F	CGAGATCAATTTACGGGGAATA	582	58	(18)
	QnrD.R	AACAAGCTGAAGCGCCTG			
oqxA	OqxA.F	GACAGCGTCGCACAGAATG	339	61	(21)
	OqxA.R	GGAGACGAGGTTGGTATGGA			
oqxB	OqxA.F	CGAAGAAAGACCTCCCTACCC	240	61	(21)
	OqxA.R	CGCCGCCAATGAGATACA			
*qep*A	QepA.F	GCAGGTCCAGCAGCGGGTAG	218	60	(20)
	QepA.R	CTTCCTGCCCGAGTATCGTG			
aac (6')Ib-cr	AAC.F	ATGACTGAGCATGACCTTGC	519	55	(19)
	AAC.R	TTAGGCATCACTGCGTGTTC			
parC	ParC.F	TGCGTTGCCGTTTATTGG	470	56	(16)
	ParC.R	GCAGGTTATGCGGTGGAAT			
gyrA	GyrA.F	GCGATGTCGGTCATTGTT	490	56	(16)
	GyrA.R	ACTTCCGTCAGGTTGTGC			

Bp: Base Pair; F: Forward; R; Reverse

Detection of chromosomal mutations in the QRDRs

Mutations within the *gyrA* and *parC* genes of the FQ-resistant isolates were identified through amplification and sequencing of the QRDRs (16). First, the *gyrA* and *parC* genes were amplified by PCR using the primers listed in Table 1. Eventually, sequencing of the PCR products was performed with an ABI 3730XL DNA analyzer (Macrogen Inc., Korea). Nucleotide sequences were compared with reference sequences using the BLAST tools of the National Center for Biotechnology Information GenBank database (NCBI; http://www.ncbi.nlm.nih.gov/blast).http://www.ncbi.nlm.nih.gov/blast

Detection of the PMQR genes

Detection of the PMQR genes *qnrA*, *qnrB*, *qnrS*, *qnrC*, *qnrD*, and *aac (6')-Ib-cr* was accomplished using previously described PCR methods (17-20).

Detection of the efflux pump genes

The efflux pump-encoding genes *oqxA*, *oqxB*, and *qepA* were detected by PCR using specific primers, as described previously (20,21).

In the PCR process, isolates with target genes confirmed by sequencing were used as positive controls, and isolates without the target gene were used as negative controls.

Statistical analysis

Statistical analysis of the data was carried out using R software version 3.3.3 and interpreted based on prevalence distribution and percentages. Data with a p-value less than or equal to 0.05 were regarded as statistically significant.

Results

Distribution of FQ resistance in the *E. coli* isolates

In this study, 200 *E. coli* isolates were obtained from patients aged 15 to 85 years. Female patients accounted for 57.8% (n = 115/200), compared with 42% (n = 85/200) among males. Of the 200 *E. coli* isolates, 47.5% (n = 95/200) were resistant to both NA and CIP, categorizing them as FQ-resistant. Approximately 75% (n = 71/95) of the *E. coli* isolates had CIP MIC ≥ 32 µg/mL, with 25% of isolates (n = 24/95) having MIC 4 - 6 µg/mL. Among the 95 FQ-resistant *E. coli* isolates, 30% (n = 29/95) were screened as the ST131 clone using PCR assay. All screened ST131 isolates belonged to the O25 serotype, also known as the O25-ST131 clone. High-level CIP resistance (MIC ≥ 32 mg/L) was found in 96.5% (n = 28/29) of ST131 and 65% (n = 43/66) of non-ST131 isolates (p = 0.001). The remaining 24 FQ-resistant isolates exhibited low-level CIP resistance (MIC 4 - 16 µg/mL).

Mutations in *gyrA* and *parC*

DNA sequence analysis of the QRDRs of *gyrA* and *parC*, shown in Table 2, revealed that the FQ-resistant *E. coli* isolates had two mutation types in *gyrA* and three in *parC*. Point mutations in *gyrA* occurred at positions 83 (Serine → Leucine) and 87 (Aspartic acid → Asparagine). In *parC*, mutations were found at positions 80 (Serine → Isoleucine), 84 (Glutamic acid → Valine), and 84 (Glutamic acid → Glycine). Single mutations S83L and D87N in *gyrA* were found in 20% (n = 19) and 11.5% (n = 11) of the FQ-resistant isolates, respectively. Single mutations identified in *parC* were S80I, E84V, and E84G, occurring in 10.5% (n = 10), 23% (n = 22), and 4% (n = 4) of the FQ-resistant isolates, respectively. Mutations in *gyrA* (Single or Double) within QRDRs were most frequently observed in 96% (n = 28/29) of ST131 and 82% (n = 54/66) of non-ST131 isolates (p = 0.05). Double amino acid substitutions in *gyrA* and *parC* were identified in 89% (n = 85/95) of FQ-resistant isolates; these substitutions were observed in 53.6% (n = 51/95) in the *gyrA* gene compared with 35.6% (n = 34/95) in the *parC* gene (p = 0.01). Comparative analysis revealed a significant difference in the presence of double mutations, S80I + E84V in *gyrA* (76% ST131 vs. 43% non-ST131; p = 0.004) and S80I + E84V in *parC* (55% ST131 vs. 26% non-ST131; p = 0.002). Isolates with double mutations exhibited significantly higher levels of CIP resistance (p ≤ 0.05). Among the FQ-resistant isolates, six non-ST131 isolates had a wild-type QRDR, while the remaining isolates (n = 89/95, 93.6%) had amino acid exchanges in one or both *gyrA* or *parC* genes.

Prevalence of PMQR resistance genes and the *aac (6')-Ib-cr* variant

Table 2 shows the prevalence of FQ resistance genes in FQ-resistant *E. coli* isolates; 74.7% (n = 71/95) of isolates possessed at least one PMQR

gene. The most common PMQR gene was *qnrS*, which was found in 42% (n = 40/95) of *E. coli* isolates, followed by *aac* (*6′*)-*Ib-cr* (n = 35/95; 36%), *qnrB* (n = 15/95; 16%), *qnrC* (n = 5/95; 5.2%), and *qnrD* (n= 1/95; 1%). The *qnrA* gene was not found in any of the FQ-resistant E. coli isolates. The *aac* (*6′*)-*Ib-cr* and *qnrS* genes were the most frequently observed PMQR genes in ST131 (n = 16/29, 55%) and non-ST131 isolates (n = 28/66, 42%). Statistical analysis indicated a significant relationship between the presence of *aac* (*6′*)-*Ib-cr* and the ST131 clone compared with non-ST131 ($p < 0.03$).

Twelve ST131 isolates carried more than one PMQR gene in the following combinations: *qnrS* + *qnrB* (n = 2), *qnrS* + *qnrD* (n = 1), *qnrS* + *aac* (*6′*)-*Ib-cr* (n = 5), *qnrS* + *qnrB* + *aac* (*6′*)-*Ib-cr* (n = 2), and *qnrS* + *qnrC* + *aac* (*6′*)-*Ib-cr* (n = 2). In contrast, the combinations of PMQR genes in 18 non-ST131 isolates were as follows: *qnrS* + *qnrB* (n = 7), *qnrB* + *aac* (*6′*)-*Ib-cr* (n = 2), *qnrS* + *aac* (*6′*)-*Ib-cr* (n = 4), *qnrB* + *aac* (*6′*)-*Ib-cr* (n = 3), *qnrS* + *qnrB* + *aac* (*6′*)-*Ib-cr* (n = 1), and *qnrS* + *qnrC* + *aac* (*6′*)-*Ib-cr* (n = 1).

Prevalence of efflux pump genes

In FQ-resistant *E. coli* isolates, 37% (n = 35/95) were positive for at least one of the three efflux pump genes: *qepA* (n = 11/95, 11.5%), *oqxA* (n = 27/95, 28%), and *oqxB* (n = 13/95, 13.5%). Notably, *oqxA* had the highest prevalence in both ST131 (n = 11/29; 38%) and non-ST131 (n=16/66; 24%) isolates.

Table 2. Prevalence of the FQ resistance genes in the FQ-resistant E. coli isolates

n (%) of the FQ-R genes in the *E. coli* isolates			
Resistance genes	**ST131 clone; n=29**	**Non-ST131 clone; n=66**	**P-value***
Mutations in the QRDR			
Mutation in *gyrA*			
S83L: Ser83Leu	4 (10)	16 (24)	0.19
D87N: Asp87Asn	2 (6.8)	9 (13)	0.28
S83L+ D87N	22 (75)	29 (43)	0.004
Mutation in *parC*			
S80I: Ser80Ile	2 (7)	8 (14)	0.35
E84V: Glu84Val	4 (3)	18 (27)	0.11
E84G: Glu84Gly	0	4 (6)	0.51
S80I+ E84V	16 (55)	15 (26)	0.004
S80I+ E84G	0	3 (4.5)	0.48
PMQR genes			
Quinolone-encoding *qnr* and *aac* (*6′*)-*Ib-cr* genes			
qnrS	12 (41)	28 (42)	0.55
qnrB	4 (13.7)	11 (16.6)	0.47
qnrC	3 (10%)	2 (3)	0.16
qnrD	1 (%)	0	0.52
aac (*6′*)-*Ib-cr*	16 (55)	19 (28)	0.02
Efflux pumps-encoding genes			
qepA	3 (10%)	8 (12%)	0.55
oqxA	11 (38%)	16 (24%)	0.13
oqxB	6 (20%)	7 (10%)	0.16

n: Number; FQ-R: Fluoroquinolone Resistance; QRDR: Quinolone Resistance-Determining Regions; PMQR: Plasmid-Mediated Quinolone Resistance.
*A p-value less than or equal to 0.05 is typically considered to be statistically significant.

Discussion

FQs are a class of antibiotics commonly used to treat UTIs. The rise and distribution of FQ-resistant *E. coli* strains-especially the ST131 clone-represent a major public health concern because of their strong capacity for widespread international dissemination (22,23). This study screened the prevalence of *E. coli* ST131 and FQ resistance genes in patients with UTIs.

Identifying how common these resistance determinants are and how they are distributed is essential for selecting suitable antibiotics and strengthening infection control strategies. In the current study, the FQ resistance rate in *E. coli* isolates exceeded 47.5%. Damavandi et al. observed 48% FQ resistance in *E. coli* isolates obtained from inpatients, which is very close to the present research (24). The prevalence of FQ resistance varies across different countries, with rates reported as 20 - 30% in Turkey, 62.25% in China, 51.8% in Pakistan, and 55.6% in Iran (25-28). Variations in reported FQ resistance rates among *E. coli* isolates can be attributed to factors such as local antibiotic-prescribing habits, infection control quality, and circulation of high-risk lineages such as ST131 (29). Our study found that the ST131 clone accounted for 30% (n = 29/95) of FQ-resistant isolates, regardless of whether the isolates produced extended-spectrum beta-lactamases (ESBLs). Raoulinasab et al. reported that among FQ-resistant isolates producing ESBLs, 55% (n = 30/60) belonged to the ST131 clone (30).

FQ antibiotics exert their bactericidal effects by inhibiting DNA gyrase and topoisomerase IV, enzymes essential for bacterial DNA replication. However, the primary target of these antibiotics can vary depending on the bacterial species and the type of FQ used (31,32). This study demonstrated a significantly higher prevalence of mutations in the *gyrA* gene compared with the *parC* gene. Moreover, double mutations within *gyrA* (53.6%) were also significantly more frequent than double mutations in *parC* (35.6%; p = 0.01). Research evaluating *E. coli* isolates carrying mutations in both enzymes indicates that DNA gyrase is typically the main target of fluoroquinolones and is more readily inhibited by these drugs. Topoisomerase IV appears to play a secondary role. Consequently, mutations in the *gyrA* gene, which codes for the gyrase A subunit, often confer initial resistance to FQs. In contrast, mutations in *parC*, encoding topoisomerase IV subunits, typically arise later during the development of multidrug resistance (33). There are few reports evaluating FQ resistance genes in the ST131 clone (30,34,35). The current study showed a significantly higher frequency of double mutations in *gyrA* (S83L and D87N) and *parC* (S80I and E84V) among ST131 isolates compared with non-ST131 isolates. In a study conducted in Iran, a significant frequency (80%) of double mutations in *parC* was observed in ST131 isolates (30). The emergence of double mutations in the ST131 clone highlights the urgent need for comprehensive strategies to prevent the spread of these extensively drug-resistant strains, including rigorous surveillance, infection control protocols, and antibiotic stewardship programs. The substitution E84G in *parC* was not observed in any ST131 isolates, consistent with the findings of previous studies (30,34). Chromosomal mutations lead to alterations in topoisomerase enzymes, rendering them less susceptible to the inhibitory effects of ciprofloxacin. In the present study, E-test MIC experiments revealed high-level ciprofloxacin resistance (MIC ≥ 32 µg/mL) in 96.6% (28/29) of ST131 isolates compared with 65% (43/66) of non-ST131 isolates, and this difference was statistically significant (p = 0.001). The higher frequency of double mutations in the *gyrA* and *parC* genes within ST131 isolates may explain this disparity. Consistent with our findings, a previous study from Iran reported that all ST131 isolates exhibited MIC ≥ 32 µg/mL to ciprofloxacin (30). Interestingly, six non-ST131 bacteria with wild-type QRDR had low levels of ciprofloxacin resistance in our study.

PMQR genes are another FQ resistance mechanism. Among the FQ-resistant *E. coli* isolates, 74.7% harbored at least one PMQR gene, *qnr* or *aac* (*6′*)-*Ib-cr*. The *qnrS* gene emerged as the most prevalent in 63% of FQ-resistant isolates. The *aac* (*6′*)-*Ib-cr* and *qnrS* genes were the most frequently occurring PMQR genes in ST131 (n = 16, 55%) and non-ST131 isolates (n = 28, 42%). Statistical analysis indicated a significant relationship between the presence of *aac* (*6′*)-*Ib-cr* and the ST131 clone (62%; $p < 0.03$). In a study in Mexico, similar to our study, 100% (n = 14/14) of O25-ST131 lineage isolates had *aac* (*6′*)-*Ib-cr*, and 7% (n = 1/14) had *qnr*A1 (35). The significant association ($p < 0.03$) of the *aac* (*6′*)-*Ib-cr* gene with the ST131 lineage in this study suggests a potential role for this gene in FQ resistance. Further research is needed to elucidate the specific contribution of *aac* (*6′*)-*Ib-cr* to fluoroquinolone resistance in ST131. The *aac* (*6′*)-*Ib-cr* enzyme, as a bifunctional acetyltransferase, can modify aminoglycosides and quinolones simultaneously, conferring resistance to clinically relevant aminoglycosides (36,37).

In these multidrug-resistant (MDR) bacteria, efflux pumps work overtime to push antibiotics out of the cell, lowering the concentration of the drug inside and making the bacteria less susceptible (38). The spread of efflux pump genes such as *oqxAB* among bacteria raises

serious concerns for public health (39). Our results showed that 37% of FQ-resistant isolates were positive for at least one *oqxA*, *oqxB*, or *qepA* gene, with *oqxA* being the most prevalent efflux pump gene (28%). ST131 isolates exhibited a higher prevalence of *oqxA* and *oqxB* genes compared with non-ST131 isolates; however, this difference was not statistically significant ($p > 0.05$). In another study in Iran, the most common FQ resistance efflux pump genes were *oqxB* (34%), followed by *oqxA* (25%) and *qnrB* (18%) (40). The results highlight the need for continuous monitoring of quinolone resistance determinants to minimize the emergence and selection of high-risk *E. coli* clones showing reduced susceptibility or resistance to quinolones.

The limitation of our study is that further surveys should include different resistance genes and more isolates using different laboratory methods.

Conclusion

This study revealed a worrying prevalence of FQ-resistant *E. coli*, particularly within the ST131 clone, highlighting the need for continuous monitoring to inform infection control strategies and minimize the spread of these resistant strains. The high frequency of mutations in *gyrA* and the presence of PMQR genes such as *aac* (*6′*)-*Ib-cr* were alarming indicators of FQ resistance. In addition, the significant association between double mutations and the *aac* (*6′*)-*Ib-cr* gene with the ST131 lineage warrants further investigation in resistance development.

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Ethical Statement

This study was approved by the Islamic Azad University, Jahrom Branch, Iran (NO. p-162376730).

Conflicts of Interest

The authors declare they have no conflicts of interest.

Author Contributions

Mehdi Bozorgi Mazandarani, Mohammad Kargar, and Farshid Kafilzadeh supervised the study, collected samples, performed the work, and wrote and edited the manuscript.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing does not apply to this article.

Use of Artificial Intelligence

The authors confirm that no artificial intelligence tools were used, either directly or indirectly, in the preparation of this article.

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