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ORIGINAL RESEARCH

Genomic Characterization and Antimicrobial Resistance of ESBL-Producing, *Escherichia coli* Isolates in Suzhou, China

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Background: The prevalence of third-generation cephalosporin-resistant and extended-spectrum beta-lactamases (ESBL) producing *Escherichia coli* poses a significant global public health concern due to their resistance to multiple antibiotics; however, their prevalence and epidemiological patterns in China are not very well investigated.

Objective: This study aimed to investigate the molecular epidemiology, and antimicrobial susceptibility of ESBL-producing *E. coli* among clinical isolates in China.

Methods: Phenotypic ESBL-producing *E. coli* isolates were collected from in-patients at a non-tertiary hospital in Suzhou from 2018.06.01 −2019.11.30. All isolates were identified and analyzed by conventional microbiological methods, and antimicrobial susceptibility testing was determined. Genes associated with resistance to *β*-lactamases, fluoroquinolone, aminoglycosides, sulfonamides, sequence types (STs), and genetic relationship were characterized through whole-genome sequencing (WGS) data.

Results: Eighty-six isolates were collected and sequenced, and genomic analysis identified twenty-five different sequence types (STs). The most prevalent STs were ST131 (n=22, 25.6%), ST1193 (n=16, 18.6%), ST38 (n=9, 10.5%) and ST167 (n=6, 7.0%). *bla*CTX-M genotypes were the most dominant, comprising a variety of subtypes (eg, *bla*CTX-M-14, *bla*CTX-M-15, *bla*CTX-M-27, *bla*CTX-M-55) and *bla*TEM-type among ESBL-producing *E. coli* in our study. All cases of co-carriage of *β*-lactamase genes showed a strong link to amoxicillin/sulbactam resistance, while the co-carriage of *bla*CTX-M-15/TEM-1B or *bla*CTX-M-15/OXA-1 were strongly linked to resistance against cefepime, ceftazidime, and aztreonam. In addition, genes associated with resistance to fluoroquinolone, aminoglycosides, and sulfonamides were also detected.

Conclusion: Our findings highlighted the prevalence of globally circulating ESBL-producing *E. coli* clones, such as ST131 and ST1193, in Suzhou, China. These clones and sublineages are also resistant to quinolones. No predominant *bla*CTX-M subtypes were detected, while the coexistence of different ESBL types was strongly linked to resistance to amoxicillin/sulbactam, cefepime, ceftazidime, and aztreonam, suggesting the widespread circulation of diverse *bla*CTX-M genes within the Suzhou community. In clinical cases of ESBL resistance, carbapenem therapy is recommended as most (>90%) isolates were susceptible.

Keywords: antimicrobial resistance, *Escherichia coli*, extended spectrum *β*-lactamase, whole-genome sequencing

Introduction

Antimicrobial resistance (AMR) is a major global public health and challenge in the management of bacteria infection.[1] Among the increasing spread of multidrug-resistant (MDR) Gram-negative bacteria, *Escherichia coli*, is the leading cause of community and hospital infections. The challenge of AMR in East Asia and Southeast Asia are similar to those observed globally, and China is considered as a hotspot for AMR emergence because of the misuse or overuse of antibiotics for humans without prescription despite the regulations and the high antimicrobial usage for

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livestock.[1,2] *E. coli* has gained significant attention due to its ability to carry various *β*-lactamases. *β*-lactamases are enzymes that confer resistance to *β*-lactam antibiotics and are often associated with co-resistance to other antibiotic classes, such as fluoroquinolones, aminoglycosides, and sulfonamides, which contributes to the increasing resistance to these agents.[3]

The genetic background of such resistance has been extensively studied worldwide. Currently, there are more than 265 *bla*CTX-M variants. The global dissemination of extended-spectrum β-lactamase (ESBL)-producing *E. coli* is mainly driven by the *E. coli* ST131 (ST: sequence type), which carries the *bla*CTX-M-15 gene.[4] Its high prevalence is often associated with resistance against third-generation cephalosporin. In contrast, other members of the *bla*CTX-M family, such as *bla*CTX-M-9, *bla*CTX-M-14, *bla*CTX-M-27, and *bla*CTX-M-28, are less frequently identified but still contribute to the global challenge of antibiotic resistance. They often vary in specific geographic location or communities, emphasizing the importance of monitoring for the spread of multidrug resistant (MDR) pathogens.[3] The advancements in whole-genome sequencing (WGS) technology have revolutionized the field of microbial genomics and antimicrobial resistance surveillance. A detailed molecular study on the genomic plasticity of ESBL producing *E. coli* has been made possible using WGS data, which are useful for identifying changing mechanisms of resistance, alternative drug targets, and to infer transmission routes to control pathogenicity.

Many studies in China have already demonstrated that ESBL-producing *E. coli* in tertiary and county hospitals is becoming an epidemic.[5–7] Liao et al investigated the molecular characteristics of 127 clinical ESBL-producing *E. coli* isolates collected from 9 hospitals in 9 regions around China by conventional PCR and Sanger sequencing, and the results indicated that AMR-type ESBLs, particularly CTX-M-14/15/55 are the most prevalent ESBLs in China.[7] However, most studies focused on emerging clones and well-known AMR gene families using a targeted PCR approach, and limited genomic data are available to characterize the prevalence of sequence types and ESBL gene families among *E. coli* in China, particularly in Jiangsu Province. In this study, we aim to explore the epidemiology, microbiological, and genomic characteristics of ESBL producing *E. coli* infections in adults admitted to non-tertiary hospital between 2018.06.01 and 2019.11.30 in Suzhou, China.

Methods and Materials

Study Population

People's Hospital of Suzhou New District (SND) is a non-tertiary hospital located in Suzhou, China, with 800 beds for adult patients. Clinical specimens were collected from in-patients suspected with bacterial infection in people's hospital of SND during the period 2018.06.01 −2019.11.30. Each sample was processed following conventional microbiological analyses protocols, and all *E. coli* were isolated and identified at species level by the VITEK2 system (bioMérieux, France) and confirmed by MALDI-TOF/MS (Autof MS1000 China). The study was conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the Ethics Committee of the People's Hospital of Suzhou New District (The IRB ethics number: 2019-111). All participants signed an informed consent to the investigation.

Antimicrobial Susceptibility Testing

All non-duplicate clinical isolates of *E. coli* with resistance to cefotaxime [minimum inhibitory concentration (MIC) > 2 mg/L] or ceftazidime MIC >4 mg/L were retrospectively tested for ESBL production using the VITEK 2 system (bioMérieux, France).

The susceptibility to 15 antimicrobial agents (ceftazidime, cefepime, ertapenem, imipenem, aztreonam, cefotetan, ampicillin-sulbactam, piperacillin-tazobactam, ciprofloxacin, levofloxacin, gentamicin, amikacin, tobramycin, trimethoprim and sulfamethoxazole and nitrofurantoin) was determined using the VITEK 2 system (bioMérieux, France), along with the corresponding AST-GN13 cards. The CLSI guidelines (2018 or 2019 accordingly) were adopted for the interpretation of MICs for antimicrobial susceptibilities. *Escherichia coli* ATCC 25922 was used as the quality control strain.

Whole-Genome Sequencing and Bioinformatics Analysis

Whole-genome sequencing was performed at Shanghai Biozeron Biotechnology Co., Ltd. (Shanghai, China). In brief, genomic DNA was extracted from cell pellets using a Bacteria DNA Kit (Omega, Bio-tek) according to the manufacturer's instructions. Genomic DNA was quantified using a TBS-380 fluorometer (Turner BioSystems Inc., Sunnyvale, CA). High-quality DNA samples (OD260/280=1.8–2.0, >6μg) were used to construct the library; at least 1μg of DNA was used for Illumina DNA prep library construction. Paired-end libraries with insert sizes of approximately 400 bp were prepared following standard genomic DNA library preparation procedures. Sequencing was performed on the Illumina HiSeq 4000.

The prediction of sequence types (STs) and genes encoding resistance to β-lactams, fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole (Cotrimoxazole) was performed using MLST and the ResFinder v3.2 software implemented in Abricate (https://github.com/tseemann/abricate) (parameters: min_cov 70%, min_id 70%). The mutations in the quinolone resistance-determining region (QRDR) were characterized using AMRFinderplus v3.8.[8] Plasmid determination and classification were based on the PlasmidFinder v2.1 database (parameters: min_cov 70%, min_id 70%). FimH type was determined using FimTyper1.0 available on the Center for Genomic Epidemiology website (https://www.genomicepidemiology.org/). The genetic relatedness of *Escherichia coli* isolates was inferred based on core genome single nucleotide polymorphisms (SNPs) using Parsnp (NC 011750.1 as reference genome).[9] Of which core genome SNPs were detected from the genomes using MUMs (maximal unique matches) and aligned with lib-MUSCLE, and a phylogenetic tree was built using FastTree in the pipeline.[9] The relationship of the isolates was visualized via iTOL.[10]

Results

Eighty-six ESBL-producing *E. coli* isolates were collected mainly from clinical specimens, including urine (n=53, 62.3%), sputum (n=15, 17.6%), feces (n=7, 8.2%), vaginal discharge (n=4, 4.7%), blood (n=3, 3.5%), and other specimens (n=4) from different clinical departments (Table S1).

All isolates were resistant to ampicillin, cefazolin and ceftriaxone, while 44.2% isolates were resistant to ceftazidime, 26.7% isolates to cefepime (Figure 1, Tables S2a and S2b). Resistant to aztreonam was observed in 69.8% of the isolates, and 54.7% of isolates were resistant to ampicillin/sulbactam. However, the *E. coli* isolates exhibited low resistance rates against piperacillin/tazobactam (4.7%). Resistance to ciprofloxacin and levofloxacin was 74.4% and 62.8%, respectively. For aminoglycosides, 44.2% and 17.4% of isolates were resistant to gentamicin and tobramycin, respectively. The isolates also displayed low resistance rates (2.3%) to ertapenem, imipenem, and amikacin. All isolates were susceptible to nitrofurantoin. Multidrug-resistance (≥ three different class of antibiotics) was found in 85.9% ESBL *E. coli* isolates, and a strong link between *β* -lactams and QR (quinolone resistance) was observed, with 75.5% of these ESBL isolates being resistant to quinolones, while with 47.6% of these ESBL isolates being resistant to aminoglycosides.

Most samples were sequenced with great depth (>100X); the coverage for each sample ranged from 82–248X (Table S3). From the genome assembly data, twenty-five STs were identified among the 86 isolates of ESBL-producing *E. coli*. The four most prevalent STs were ST131 (n=22, 25.6%), followed by ST1193 (n=16, 18.6%), ST38 (n=9, 10.5%) and ST167 (n=6, 7.0%) (Figure S1). The core genome SNP alignment contained 2,876,028 bp, and genetic variation was detected in prevalent STs, for example, ST131 isolates were divided into two sub-lineages, and the SNPs variation ranged from 1 to 270 in sub-lineage 1, and 26–681 sub-lineage 2 (Figure 2 and Table S4). Similarly, ST1193 differed from 2 to 339 SNPs. Subtyping based on FimH revealed 19 subtypes, and eight isolates were not typable. FimH30 was most frequently typed among ST131 isolates (11 [50%] of 22) followed by FimH41 (10 [45.5%] of 22), FimH64 among ST1193 isolates (100%, 16 of 16), and FimH5 among ST38 isolates (8 [52%] of 9) (Table S3).

All 86 isolates of ESBL-producing *E. coli* carried the *β*-lactamase genes (Figure 2 and Table S3). The predominant ESBL gene was *bla*CTX-M-14 (n=21, 14%), followed by *bla*CTX-M-15 (n=20, 13.3%), *bla*CTX-M-27 (n=18, 12%), *bla*CTX-M-55 (n=15, 10%), and *bla*CTX-M-65 (n=7, 4.7%). Other *β*-lactamases included *bla*OXA-1 (n=10, 11.6%) and *bla*TEM-1B (n=36, 24%) (Table S3). Among ST131-*H*30 isolates (n=11), five carried *bla*CTX-M-15 (Table S3). Sixty-five percent (45/86) of isolates co-produced one or more *β*-lactamases. All cases of co-carriage of *β*-lactamase genes

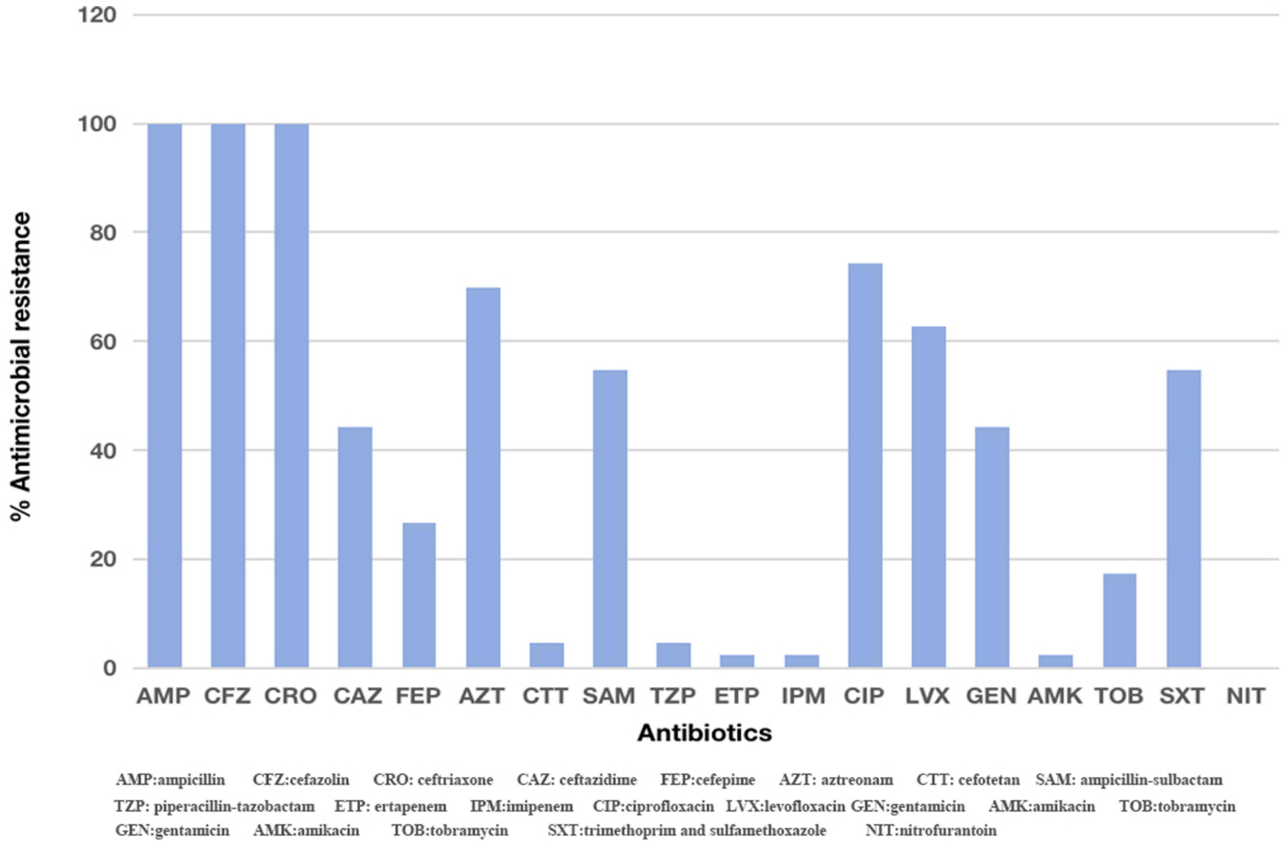

Figure 1 Antimicrobial susceptibility profiles of 86 isolates of ESBL-producing *E. coli* to 15 antibiotic agents.

showed a strong link to amoxicillin/sulbactam resistance, while co-carriage of *bla*CTX-M-15/TEM-1B or *bla*CTX-M-15/OXA-1 was strongly associated with resistance to cefepime, ceftazidime, and aztreonam (P<0.01).

All 86 isolates carried resistance genes related to more than one antibiotic group, including fluoroquinolones, aminoglycosides and sulfonamides (Figure 2 and Table S3). Mutations in quinolone resistance-determining regions (QRDR) such as chromosomal *gyrA, parC*, and *parE* were detected in 98.7% (78/79) of fluoroquinolone-resistant *E. coli* isolates, while they were detected in 14.3% (1/7) of fluoroquinolone-susceptible *E. coli* isolates, with S83L (n = 77) and S80I (n = 56) being the most common (Figure 2 and Table S5).

At least one plasmid-mediated quinolone resistance (PMQR) gene was detected in 21 (21/78, 27%) fluoroquinolone-resistant *E. coli* isolates, including *qnrS* in 12 isolates (12/86, 14%), *aac(6')-Ib-cr* in 10 isolates (10/86, 11.6%), and *oqxA*/*oqxB* in one isolate. PMQR genes were also found in one isolate of fluoroquinolone-susceptible *E. coli* carrying *qnrS1*. Additionally, 18 (18/78, 23%) isolate of fluoroquinolone-resistant *E. coli* carried both QRDR mutations and PMQR genes, with *aac(6')-Ib-cr* found in 10 isolates co-carrying QRDR mutations and *qnrS1* in 9 isolates co-carrying QRDR mutations (Figure 2 and Table S5). The most prevalent *E. coli* ST was ST131 (approximately 25% of the collection). Resistance to fluoroquinolones was significantly higher in ST131 isolates (86.3%; 19/22). Five QRDR mutations were detected: *gyrA* (S83L and D87N), *parC* (S80I and E84V), and *parE* (I529L) in 57.9% (11/22) of the isolates (ST131-*H*30 lineage). In contrast, fluoroquinolone-susceptible *E. coli* ST131 isolates had only *gyrA* (S83L) and *parE* (I529L) mutations in 3 isolates (Figure 2 and Table S5).

The second most prevalent *E. coli* STs, resistance to fluoroquinolones was particularly in ST1193 isolates (16/16,100%) which all harbored the same mutations in *gyrA* (S83L and D87N), *parC* (S80I) and *parE* (L416F) (Table S3).

Eight different aminoglycoside-modifying enzyme genes were detected. Ninety-two percentage (35/38) and 83% (34/41) of isolates resistance to gentamicin and tobramycin, respectively, harbored *aac(3)-II* genes, in contrast, only 2 in 48 isolates susceptible to gentamicin carried *aac(3)-II* genes, similar as tobramycin. Two isolates with high-level resistance

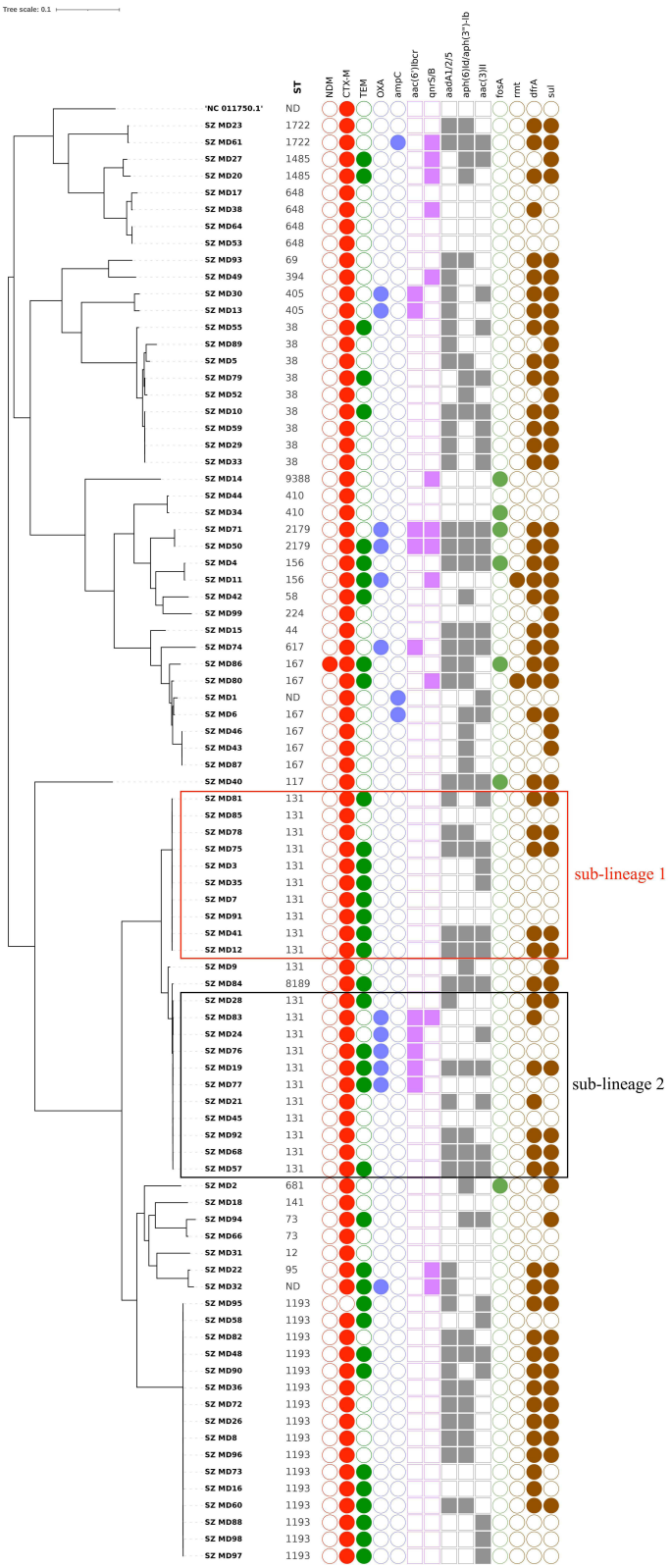

Figure 2 Genetic relationship of ESBL-producing *E. coli* isolates inferred from core genome SNPs overlaid with sequence types and major antimicrobial resistant genes.

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to amikacin carried 16S rRNA methylase genes (two *rmtB*). No difference was observed in carrying *addA* and *aph(6)-Id*/*aph (3")-Ib* between resistant isolates and susceptible isolates to gentamicin and tobramycin. Genes encoding fosfomycin-modifying enzymes (fos genes) were detected in 7 isolates (7/86, 8.1%) (Figure 2 and Table S3).

Among the 86 isolates, 44 carried *sul1*, 43 carried *sul2*, and 2 carried *sul3*. Thirty-one isolates co-carrying *sul1* and *sul2*, 79% (37/47) and 77% (36/47) resistant isolates to sulfamethoxazole/trimethoprim (SXT) carried sul1 and sul2, respectively, which co-carrying sul1and sul2 consist of 29 (62%), by contrast, 18% (7/39) susceptible isolates to SXT carried *sul1* and *sul2,* respectively, no co-carrying sul1 and sul2 was detected among SXT susceptible isolates. Lastly, the main trimethoprim resistance genes detected were *dfrA17* (n=44), followed by *dfrA14* (n=7). The *dfrA* genes presented in 45/47% of the resistance to SXT isolates, and 10/39 susceptible to SXT isolates, co-carriage of *sul1* or *sul2* with one of the trimethoprim resistance genes (*dfrA*) was observed in 91% (43/47) isolates and was correlated with phenotypic SXT resistance. Of note, one of the two carbapenem-resistant isolates carried the carbapenemase NDM-5 (Table S3).

Discussion

The proportion of ESBL-producing *E. coli* among different specimens in our study is consistent with previous studies reporting a high prevalence of ESBL in urine samples.[6,11] However, sputum (15, 17.6%) is the second most frequent source, followed by feces, while blood is the least frequent source in our patient population. This differs from a study conducted in Guangzhou, which identified a high prevalence of ESBL-producing *E. coli* in blood samples.[6] This discrepancy may be attributed to the high frequency of urinary tract infections (UTIs) and chronic respiratory infections among elderly patients at non-tertiary hospitals.

All *E. coli* isolates in this collection were phenotypically resistant to *β*-lactams, with over 40% of the isolates resistant to at least one another antibiotic class such as fluoroquinolones, aminoglycosides, and sulfonamides, which is consistent with the previous report from Guangdong in China.[6]

Many studies have shown that ESBL-producing *E. coli* frequently belong to ST131 and to a lesser extent to ST38, ST405, ST648 or other STs in clinical specimens.[12] For example, community infection studies in the USA and UK found that 53% and 64% of ESBL-producing *E. coli* were ST131, respectively.[13,14] However, in our study, although the *E. coli* isolates were collected from different departments within one hospital, the STs revealed considerable genetic diversity. ST131 accounted for 25% of the isolates, while other sequence types included ST1193 representing 18% and ST38 representing 10%. Similarly, previous studies in tertiary and county hospitals in China have also shown that ST131 was found in 12.7% and 13.4% of ESBL-producing *E. coli,* respectively, indicating that no predominant ESBL-producing *E. coli* ST epidemic was found in China.[15,16] Half of ST131 isolates (11/22) belonged to ST131-*H*30 (sub-lineage 2), which has been the global disseminated lineage associated with fluoroquinolone resistance, and five ST131-*H*30 isolates, with CTX-M-15 belonged to subclade ST131-*H*30Rx, which is considered the main driver for the spread of ESBL CTX-M.[17] The ratio of *H*30 lineage in ST131 in this investigation was lower than a former study in Fujian using PCR-based technique, in which 63.9% (53 out of 86) of ST131 isolates belong to *H*30 lineage, while the remaining belonged to *H*41 lineage.[18] However, out of 53 ST131-H30, only 13 belonged to H30Rx.[18] Another study among urinary tract infection (UTI) in women in Changsha indicated that 92.6% of ST131 isolates belonged to H30 subgroup.[19]

This study revealed that *bla*CTX-M genotypes were the most dominant, comprising a variety of subtypes (eg, *bla*CTX-M-14, *bla*CTX-M-15, *bla*CTX-M-27, *bla*CTX-M-55) and *bla*TEM-type ESBLs among ESBL-producing *E. coli* in our hospital population, which is consistent with findings reported previously in China.[16,20] Although *bla*CTX-M-14 and *bla*CTX-M-15 are still the most common *bla*CTX-M enzymes globally, *bla*CTX-M-27, a single-nucleotide variant of *bla*CTX-M-14, has begun to out-compete other *bla*CTX-M genotypes and is now found worldwide (in Japan, China, Southeast Asia, North America, and Europe).[21] *bla*CTX-M-27 has a higher MIC for ceftazidime compared with *bla*CTX-M-14 and may also be more transmissible in a nosocomial environment compared with *bla*CTX-M-15 producers.[21] *bla*CTX-M-55, which differs from *bla*CTX-M-15 by only one amino acid mutation, is frequently detected in ESBL-producing *E. coli* originally from animals. Our results indicated that *bla*CTX-M-55 gene may have already been passed from animals to humans through the food chain. However, the transmission mechanism of drug-resistant bacteria from animals to humans is currently unclear, and further studies are required to elucidate this process.

Substitutions in the QRDR are still the major determinants of quinolone resistance. A single mutation in *gyrA* at codon 87 or in *parC* at codon 801 can lead to ciprofloxacin/levofloxacin resistance. However, a single *gyrA*83 substitution was also present in 9 of 14 ciprofloxacin/levofloxacin-susceptible isolates, which is not in agreement with previous studies reporting that *gyrA*83 substitution was the most resistant phenotypes that showed the highest level of resistance.[22] Moreover, PMQR was still rare. The frequency of ST131 isolates that were resistant to ciprofloxacin was >80% among ESBL-producing *E. coli* populations, demonstrating high multidrug-resistance of isolates in this ST, with specific substitutions in *gyrA* or *parC* as found in our study have been described previously.[23] ST1193 is the second most common ST (n=16, behind ST131) among ESBL-producing *E. coli* populations, which aligns with our results, showing that 100% of ST1193 isolates were fluoroquinolone-resistant isolates (Figure 2 and Table S5). This suggested a high resistance to quinolones, with the same distinctive mutations in tQRDR (*gyrA* S83L/D87N, *parC* S80I, and *parE* L416F) as reported previously.[24] Huang et al speculated that a particular *bla*CTX-M variants (*bla*CTX-M-55) in *E. coli* ST1193 within specific geographic regions, such as Asia including China, is mainly attributed to the clonal dissemination of *E. coli* ST1193.[24,25] However, our results revealed that various *bla*CTX-M types were present among the 16 ST1193 isolates, including *bla*CTX-M-27 (n=6), *bla*CTX-M-14 (n=3), *bla*CTX-M-55 (n=3), and *bla*CTX-M-64 (n=1). Additional studies with larger sample sizes are required to determine a potential association between ST1193 and the presence of *bla*CTX-M-55. Moreover, 75% of ST1193 isolates and 50% of ST131 isolates were found to be resistant to SXT, which is consistent with previous findings, suggesting that ST1193 and ST131 ESBL-producing *E. coli* isolates have a high rate of multidrug resistance.[26]

The coexistence of different ESBL types was also strongly linked to resistance to amoxicillin/sulbactam, cefepime, ceftazidime, and aztreonam, suggesting a high level of widespread prevalence of ESBLs among inpatients in the non-tertiary hospitals in China. These findings are consistent with previous studies in both community-associated and hospital-acquired infections in Chinese tertiary hospitals, as well as in food-producing animal settings and water, which highlights the potential need for a one-health approach to combat their spread.[27]

There are limitations in our study. This was a single center-study. Further studies are necessary with more samples from different hospitals to investigate comprehensively the molecular and antimicrobial phenotypes of *E. coli* isolates in Suzhou, China.

Conclusion

Our findings highlighted the diverse resistance patterns among ESBL-producing *E. coli* isolates within a non-tertiary hospital, particularly demonstrating the presence of multiple AMR genes such as *bla*CTX-M types, *aac(6')-Ib-cr, aac(3)-II*, and *sul* genes. Our data also confirmed the existence and circulation of ST131-*H*30 and sub-lineage ST131-*H*30Rx, which are globally disseminated ESBL-producing and fluoroquinolone resistant isolates. The coexistence of different ESBL types was also strongly linked to resistance to amoxicillin/sulbactam, cefepime, ceftazidime, aztreonam in China. This prevalence of multiple resistance determinants makes these isolates even more difficult to treat with commonly used antibiotics. Different *E. coli* STs also exhibited differences in antimicrobials resistance, suggesting that detection of the AMR genes and diagnostics tests would be helpful for guiding strategies for antibiotic use and antibiotic resistance stewardship.

Data Sharing Statement

The corresponding author can provide the datasets used and/or analyzed for this study upon reasonable request. Raw sequence reads are available on the NCBI website under BioProject accession number PRJNA796569.

Ethical Approval and Informed Consent

This study was approved by the Hospital Review Board and Ethics Committee of People's Hospital, Suzhou New District, Suzhou, Jiangsu, China.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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