

Prevalence and risk factors for colonization by extended-spectrum β -lactamase-producing or ST131 *Escherichia coli* among asymptomatic adults in community settings in Southern Taiwan

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Purpose: Fecal carriage of extended-spectrum β -lactamase-producing *Escherichia coli* (ESBL-EC) is common in Asia, especially in China and Southeast Asia. There are no data about fecal carriage of ESBL-EC and *mcr-1*-positive *E. coli* in Taiwan, and few studies focusing on the risk factors of asymptomatic fecal carriage of epidemic ST131 *E. coli* have been published.

Patients and methods: From healthy inhabitants attending health examinations at a medical center in southern Taiwan in 2017, we collected 724 stool samples, which were examined for ESBL-EC fecal carriage using chromogenic medium. ST131 and *mcr1*-positive *E. coli* were also investigated using multiplex PCR. Clinical data from all participating adults were collected to analyze the risk factors for fecal ESBL-EC or ST131 *E. coli* carriage.

Results: The prevalence rate of asymptomatic ESBL-EC fecal carriage in adults was 1.9% (14/724). ST131 was found in 22 (3.0%) adults and *mcr-1*-positive *E. coli* was found in three (0.4%) adults. A multivariate analysis showed that the risk factors associated with ESBL-EC carriage were diabetes mellitus (adjusted odds ratio [aOR]: 5.5, 95% confidence interval [CI]: 1.3–22.7), a history of colonic polyps (aOR: 6.4, 95% CI: 1.6–24.9), and chronic renal insufficiency (aOR: 20.7, 95% CI: 1.4–305.7). Underlying cancer (aOR: 4.8, 95% CI: 1.0–22.5) and stroke (aOR: 18.0, 95% CI: 1.6–207.5) were associated with ST131 *E. coli* fecal carriage. In our cohort, travel to Asian countries and food habit were not associated with ST131 or ESBL-EC fecal carriage.

Conclusions: The ESBL-EC or ST131 *E. coli* fecal carriage rate is low among asymptomatic adults in Taiwan. Certain underlying medical conditions were associated with their fecal carriage.

Keywords: fecal colonization, extended-spectrum β -lactamase, sequence type, MCR1, *Escherichia coli*

Introduction

Escherichia coli is a normal inhabitant in the human gastrointestinal tract. However, it is also an important pathogen in adults. In previous decades, the occurrence of extended-spectrum beta-lactamases (ESBL)-producing Enterobacteriaceae, which causes treatment failure of cephalosporin therapy, has become a remarkable epidemiological event. The prevalence of ESBL-*E. coli* (ESBL-EC) fecal carriage in healthy adults has been increasing alarmingly, at an annual rate of 5.4%

worldwide.¹ Recently, the prevalence of asymptomatic ESBL-EC carriage was about 5–8% in Europe, 2% in America, 6% in Japan, 19% in India, 30% in China, and 30–50% in Thailand.^{2–6} Antibiotic exposure within 6 months, daily animal contact, or travelling to Africa or Asia, had been linked to asymptomatic ESBL-EC fecal carriage.^{2–6} Colistin was considered to be the last-line antimicrobial agent for treating patients with multidrug-resistant bacteria,^{7,8} but in 2015, the plasmid-mediated colistin resistance gene, *mcr-1*, was first described in China. Since then, *mcr-1* has been identified in the environment, animals, and humans.⁷ However, there are no data on fecal carriage of ESBL-EC and *mcr-1* *E. coli* in asymptomatic people in other Asian regions including Taiwan. Moreover, few studies have focused on the risk factors for fecal carriage of ST131 *E. coli*, an epidemic strain, in the asymptomatic population. Therefore, the aims of this study were to determine the prevalence and risk factors for asymptomatic carriage of ESBL-EC, *mcr-1* *E. coli*, or ST131 *E. coli* in Taiwan.

Materials and methods

Participants

This study was conducted from April 2016 to June 2017 at the health check center in Kaohsiung Veterans General Hospital, which is located in southern Taiwan. All individuals visiting the health check center routinely fill out a standardized questionnaire, which including demographic data, personal history, medical history, and underlying chronic illness (such as peptic ulcer or colonic polyps, antibiotic therapy, or probiotic use in the past 3 months), boiled or unboiled drinking water, and diet habits.

The aforementioned data was recorded by one physician at our center during health exam interview. The participants were randomly selected and their residual fecal samples for fecal occult blood tests were collected. Only individuals whose data in the dataset of the questionnaires was intact were included in this study. Hyperuricemia was defined as a serum uric acid level ≥ 7 mg/dL,⁹ and chronic renal diseases were defined as serum creatinine >1.5 mg/dL. With a high prevalence of ESBL-EC in Asia, especially in Southeast Asia, India, and China, we also collected the participants' travel information.^{2–6} The study was approved by the Ethics Committee at the Kaohsiung Veterans General Hospital (VGHKS16-CT2-04). The ethics committee waived the need for written informed consent provided by participants due to the noninterventional and retrospective

nature of the study. Because all patient data were analyzed in anonymity, no additional informed consent was required.

Isolation of bacteria and microbiological analysis

Each stool sample was spread on a CHROMagar™ ECC plate (CHROMagar, Paris, France) and incubated at 37 °C for 24 h and up to two *E. coli* colonies were selected. If the colony color was dark pink to reddish, it was spread onto a CHROMagar™ ESBL plate (CHROMagar, Paris, France) to identify ESBL-EC isolates. ESBL genes, including *bla*_{CTX-M}, *bla*_{SHV}, *bla*_{TEM}, *bla*_{OXA-1}, *bla*_{IMP}, and *bla*_{VIM}, were assessed using the polymerase chain reaction (PCR) using previously described primers and methods,^{10–13} if ESBL-EC fecal carriage was found using chromogenic medium. PCR amplification was performed as follows: initial denaturation at 94 °C for 10 min; 30 cycles of 94 °C for 40 s, 60 °C for 40 s, and 72 °C for 1 min; and a final elongation step at 72 °C for 7 min.¹² Four *E. coli* sequence types, including ST69, ST73, ST95, and ST131, were studied using primers and a PCR method, which were previously described, with the following cycling conditions: an initial denaturation at 94 °C for 3 min; 30 cycles of 94 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s; and one final cycle of 72 °C for 5 min.¹⁴ The ESBL-EC multilocus sequence types (MLST) were confirmed by testing seven housekeeping gene sequences (*adh*, *fumC*, *gyrB*, *icd*, *mdh*, *purA*, and *recA*).¹⁰ Screening *mcr-1* in *E. coli* isolates was conducted using PCR with the primers CLR5-F (5'-CGGTCAGTCCGTTTGTTC-3') and CLR5-R (5'-CTTGGTTCGGTCTGTA GGG-3') with the initial denaturation conditions of 94 °C for 15 min; 25 cycles of 94 °C for 30 s, 58 °C for 90 s, and 72 °C for 60 s; and a final cycle of 72 °C for 10 min.⁷ ST131-positive control isolates and ESBL gene-positive and *mcr-1*-positive isolates were obtained from previous study.^{15,16}

Antimicrobial susceptibility

Cefazolin, ceftriaxone, and levofloxacin antibiotic susceptibility was measured using the disk diffusion technique on Muller-Hinton medium, according to the Clinical Laboratory Standard Institute (CLSI) guidelines.¹⁷ Antimicrobial susceptibility of ampicillin/sulbactam, piperacillin/tazobactam, cefazolin, cefmetazole, cefotaxime, ceftazidime, cefepime, ertapenem, meropenem, imipenem, amikacin, gentamycin, ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole, and tigecycline for the *mcr-1*-positive *E. coli* isolates was measured using the Vitek 2 system (Vitek AMS; bioMerieux

Vitek Systems Inc., Hazelwood, MO, USA). The minimum inhibitory concentration (MIC) of colistin was determined using the broth microdilution test and interpreted based on the 2017 CLSI guidelines.¹⁷

Statistical analysis

Categorical variables were analyzed using the chi-square and Fisher's exact tests and the independent sample *t*-test was used to analyze continuous variables in univariate analysis. Multivariable analyses in the logistic regression model were used to study risk factors of asymptomatic ESBL-EC and ST131 *E. coli* carriage. Variables with a *P*-value of ≤ 0.1 in univariate analyses were entered into a forward logistical regression analysis. *P*-values < 0.05 were considered to be statistically significant. The adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Armonk, NY, USA).

Results

During the study period, fecal occult blood tests were performed in 5,042 individuals. Among them, 743 individuals were randomly selected for enrollment and 724 participants were finally included in the study due to 19 individuals with incomplete data in the dataset of the questionnaires. There were 513 *E. coli* isolates found in the stool in the PCR study. The participants' mean age was 46.9 years, and females predominated, accounting for 52.1% of the study population. Common underlying diseases included hypertension (101/724 individuals, 14%), diabetes mellitus (31/724, 4.3%), and cancer (17/724, 2.3%). Antibiotic therapy in the previous 3 months was recalled in 8.4% (61/724) of participants. Half (367/724, 50.7%) of the participants had travelled abroad recently, including 44.6% (323/724) who travelled to Asia, 4.1% (30/724) who travelled to Europe, 5.2% (38/724) who travelled to North America, 0.4% (3/724) who travelled to Africa, and 1.2% (8/724) who travelled to Oceania. The prevalence rate of fecal ESBL-EC carriage was 1.9% (14/724) and that of ST131 *E. coli* carriage was 3.0% (22/724). Two (14.3%) of 14 ESBL-EC isolates belonged to ST131.

In the univariate analyses, two variables were associated with asymptomatic ESBL-EC fecal carriage: diabetes mellitus (OR 6.6, 95% CI 1.8–25.2) and colonic polyps (OR 6.0, 95% CI 1.6–22.5; Table 1). The multivariate logistic regression model showed that diabetes mellitus (aOR 5.5, 95% CI 1.3–22.7), colonic polyps

(aOR 6.4, 95% CI 1.6–25.0), and chronic renal insufficiency (aOR 20.7, 95% CI 0.4–305.7) were significantly associated with ESBL-EC carriage (Table 1). Among 14 isolates with the ESBL-production phenotype, six isolates had *bla*_{TEM}, six had *bla*_{SHV}, four had *bla*_{CTX-M}, one had *bla*_{VIM}, one had *bla*_{OXA-1}, and one had *bla*_{IMP} (Table 2). Five isolates had more than one ESBL gene. The major CTX-M enzyme was CTX-M-14, which was found in three isolates. Among 14 isolates of ESBL-EC, the sequence types (STs) included ST131 (n=2), S1193 (n=2), ST10 (n=1), ST38 (n=1), ST101 (n=1), ST127 (n=1), ST349 (n=1), ST410 (n=1), ST963 (n=1), ST1972 (n=1), ST2607 (n=1), and S3045 (n=1).

Underlying disease of cancer (OR 4.8, 95% CI 1.02–22.5) or stroke (OR 18.0, 95% CI 1.6–207.5) was associated with asymptomatic ST131 *E. coli* fecal carriage using the univariate analysis and multivariable logistic regression analysis (Table 3).

For antibiotic susceptibility, ST131 isolates had a higher resistance rate to cefazolin (68.2% vs 58.6%, *P*=0.380), ceftriaxone (22.7% vs 9.7%, *P*=0.070), and levofloxacin (50% vs 29.5%, *p*=0.045) than non-ST131 isolates. ESBL-EC isolates were more likely to be resistant to cefazolin (92.9% vs 57.7%, *P*=0.009), ceftriaxone (78.6% vs 7.3%, *P*<0.001), and levofloxacin (42.9% vs 30.4%, *P*=0.377) than non-ESBL-EC isolates.

mcr-1 was identified in three *E. coli* isolates, which were not ST131 or ESBL-EC. The prevalence of fecal *mcr-1 E. coli* carriage was 0.4% (3/724). Clinical characteristics of the three subjects with fecal *mcr-1 E. coli* carriage and *E. coli* isolates with colistin MICs and STs are shown in Table 4. All three subjects were healthy without chronic underlying diseases, but one had traveled to China within the past year. Three isolates were susceptible to piperacillin/tazobactam, cefazolin, cefmetazole, cefotaxime, ceftazidime, cefepime, ertapenem, meropenem, imipenem, amikacin, gentamycin, ciprofloxacin, levofloxacin, and tigecycline. The colistin MIC in three isolates was 2, 2, and 4 mg/L, respectively (Table 4).

Discussion

The prevalence and risk factors for ESBL-EC carriage in asymptomatic individuals have been described previously in many regions of the world.^{2–6} In this study, the prevalence of ESBL-EC carriage in healthy people in Taiwan was about 2%, lower than those in other areas of Asia. We found that people with a medical history of diabetes mellitus, chronic renal diseases, or colonic polyps had an

Table 1 Characteristics of 724 subjects with and without fecal extended-spectrum beta-lactamase-producing *Escherichia coli* carriage

Variables	Carriers (n=14)	Non-carriers (n=710)	Unadjusted OR (95% CI)	P-values	Adjusted OR (95% CI)	P-values
Demographic						
Age, mean ± standard deviations (years)	48.8±11.8	46.9±10.0		0.473		
Male	4 (28.6%)	343 (48.3%)	2.3 (0.7–7.5)	0.143		
Occupation in health care setting						
Diet habit	3 (21.4%)	164 (23.1%)	0.9 (0.3–3.3)	1.000		
Boiled water use	11 (78.6%)	528 (74.4%)	1.3 (0.3–4.6)	1.000		
Vegetarian	1 (7.1%)	28 (3.9%)	0.5 (0.1–4.2)	0.439		
Daily animal contact	2 (14.3%)	160 (22.5%)	0.6 (0.1–2.6)	0.746		
Travel abroad in the past 12 months						
Asia countries	8 (57.1%)	315 (44.4%)	1.6 (0.6–4.9)	0.341		
Europe	1 (7.1%)	29 (4.1%)	1.8 (0.2–14.3)	0.450		
Africa	0	3 (0.4%)		1.000		
North America	1 (7.1%)	37 (5.2%)	1.4 (0.2–11.0)	0.533		
Oceania	0	8 (1.1%)		1.000		
Medical history						
Antibiotic treatment in the past 3 months	1 (7.1%)	60 (8.5%)	0.8 (0.1–6.5)	1.000		
Probiotics use in the past 3 months	2 (14.3%)	170 (23.9%)	0.5 (0.1–2.4)	0.537		
Hypertension	2 (14.3%)	99 (13.9%)	1.0 (0.2–4.7)	1.000		
Hyperlipidemia	2 (14.3%)	71 (10.0%)	1.5 (0.3–6.8)	0.643		
Diabetes mellitus	3 (21.4%)	28 (3.9%)	6.6 (1.8–25.2)	0.019	5.5 (1.3–22.7)	0.002
Stroke	0	3 (0.4%)		1.000		
Gout or hyperuricemia	1 (7.1%)	28 (3.9%)	1.9 (0.2–14.8)	0.439		
Renal function impairment	1 (7.1%)	2 (0.3%)	27.2 (2.3–319.5)	0.057	20.7 (1.4–305.7)	0.028
Chronic hepatitis B virus infection	1 (7.1%)	86 (12.1%)	0.6 (0.1–4.3)	1.000		
Chronic hepatitis C virus infection	0	7 (1.0%)		1.000		
Colonic polyps	3 (21.4%)	31 (4.4%)	6.0 (1.6–22.5)	0.024	6.4 (1.6–25.0)	0.007
Cancer	0	17 (2.4%)		1.000		

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 2 The distribution of beta-lactamase genes in 14 *Escherichia coli* isolates with the extended-spectrum beta-lactamase-production phenotype

Isolate number	<i>bla</i> _{CTX-M}	<i>bla</i> _{TEM}	<i>bla</i> _{SHV}	<i>bla</i> _{OXA-1}	<i>bla</i> _{IMP}	<i>bla</i> _{VIM}
No. 1	-	-	+	-	-	-
No. 2	-	-	+	-	-	-
No. 3	-	+	+	+	-	-
No.4	+	+	-	-	-	-
No.5	-	-	+	-	-	-
No.6	+	-	-	-	-	-
No.7	-	+	+	-	+	-
No.8	+	+	-	-	-	+
No.9	+	+	+	-	-	-
No.10	-	+	-	-	-	-
No.11	-	-	-	-	-	-
No.12	-	-	-	-	-	-
No.13	-	-	-	-	-	-
No.14	-	-	-	-	-	-

Note: "+" indicates the presence of specific gene, and "-" indicates the absence.

increased risk of fecal ESBL-EC carriage, in accordance with earlier studies indicating that individuals with diabetes and chronic renal diseases were more likely to have ESBL-producing Enterobacteriaceae colonization or infection.^{18,19} Although a recent study suggested that gut microbes may influence the development of colonic polyps,²⁰ the relationship between colonic polyps and ESBL-EC carriage requires further confirmation. Spread of ESBL-EC in the community may be related to the transmission of ESBL-EC by food, environmental dissemination, and carriage in domestic and wild animals.²¹ However, in this study, fecal carriage of ESBL-EC was not associated with meat consumption, unboiled water use, occupation in the health care setting, or daily animal contact, and previous antibiotic use did not increase the risk of ESBL-EC carriage in asymptomatic people. These results were consistent with previous studies.^{4,6,22}

In a systemic review and meta-analysis, travelling to Asia and Africa was linked to fecal colonization with ESBL-EC,¹ which cannot be confirmed in our cohort. It is not surprising because most studies showing a positive relationship between travelling and ESBL-EC carriage were conducted in Europe and North America,²³ and our participants were Taiwanese who had more opportunities to meet Asians or visit other environments, which decreased the impact of travel on ESBL-EC carriage.

The ST131 *E. coli* clone is an important cause of fluoroquinolone-resistant *E. coli* infections,²⁴ which is consistent with our result that levofloxacin resistance was more common in ST131 *E. coli*. The emergence of ST131 in the community

would pose a challenge to empirical therapy for many community-acquired infections. ST131 transmission among people was documented after household contact with ST131 carriers,²⁵ highlighting the potential health impact of ST131 carriers. However, few studies focused on the risk factors for epidemic ST131 *E. coli* carriage in the asymptomatic population. In this study, individuals with underlying cancer or stroke had a higher risk of ST131 *E. coli* carriage. A previous study in Korea reported that ST131 was the most common sequence type of ESBL-EC bacteremia in cancer patients,²⁶ suggesting an increased susceptibility to ST131 colonization in these patients. However, to the best of our knowledge, there is no evidence suggesting that people with prior stroke had an increased risk of ST131 *E. coli* carriage; this warrants further confirmation. Moreover, we found that drinking boiled water tended to protect against ST131 *E. coli* carriage (75% vs 59%; $P=0.09$). Human ST131 carriage has been relevant to the water source of ST131 isolates.^{27,28} However, direct evidence to verify that unboiled water is the source of ST131 *E. coli* have not yet been found.

In Taiwan, *mcr-1*-harboring Enterobacteriaceae isolates have been found in patients and food-producing animals.^{8,15,29,30} A recent study including ten cases of *mcr-1*-harboring Enterobacteriaceae bacteremia revealed that 50% of them were hospitalized within 3 months before bacteremia episodes and most subjects had chronic diseases.¹⁵ Notably, all ten patients denied recent travel abroad. Characteristically, our *mcr-1*-harboring *E. coli* isolates were discovered from three asymptomatic adults without chronic diseases or recent exposure to antibiotics. The relevance of recent travel to China in

Table 3 Characteristics of 724 subjects with and without fecal ST131 *Escherichia coli* carriage

Variables	Carriers (n=22)	Non-carriers (n=702)	Unadjusted OR (95% CI)	P-values	Adjusted OR (95% CI)	P-values
Demographic data						
Age, mean ± standard deviations (years)	45.8±11.0	47.0±10.0		0.608		
Male	9 (40.9%)	338 (48.1%)	1.3 (0.6–3.2)	0.503		
Occupation in health care setting	8 (36.4%)	159 (22.7%)	2.0 (0.8–4.7)	0.133		
Diet habit						
Boiled water use	13 (59.1%)	526 (74.9%)	0.5 (0.2–1.2)	0.094		
Vegetarian	1 (4.5%)	28 (4.0%)	0.9 (0.1–6.7)	0.599		
Daily animal contact	5 (22.7%)	157 (22.4%)	1.0 (0.4–2.8)	1.000		
Travel abroad in the past 12 months						
Asia countries	7 (31.8%)	316 (45.0%)	0.6 (0.2–1.4)	0.201		
Europe	0	30 (4.3)		1.000		
Africa	0	3 (0.4%)		1.000		
North America	1 (4.5%)	37 (5.3%)	0.9 (0.1–6.5)	1.000		
Oceania	0	8 (1.1%)		1.000		
Medical history						
Antibiotic treatment in the past 3 months	2 (9.1%)	59 (8.4%)	1.1 (0.2–4.8)	0.707		
Probiotics use in the past 3 months	4 (18.2%)	168 (23.9%)	0.7 (0.2–2.1)	0.533		
Hypertension	3 (13.6%)	98 (14.0%)	1.0 (0.3–3.4)	1.000		
Hyperlipidemia	4 (18.2%)	69 (9.8%)	2.0 (0.7–6.2)	0.266		
Diabetes mellitus	1 (4.5%)	30 (4.3%)	1.1 (0.1–8.2)	1.000		
Stroke	1 (4.5%)	2 (0.3%)	16.7 (1.5–191.1)	0.089	18.0 (1.6–207.5)	0.020
Gout or hyperuricemia	2 (9.1%)	27 (3.9%)	2.5 (0.6–11.2)	0.219		
Renal function impairment	0	3 (0.4%)		1.000		
Chronic hepatitis B virus infection	1 (4.5%)	42 (6.0%)	0.3 (0.0–2.6)	0.501		
Chronic hepatitis C virus infection	0	7 (1.0%)		1.000		
Colonic polyps	1 (4.5%)	33 (4.7%)	0.5 (0.1–3.7)	1.000		
Cancer	2 (9.1%)	15 (2.1%)	4.6 (1.0–21.4)	0.091	4.8 (1.0–22.5)	0.046

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 4 Characteristics of three subjects with *mcr-1* harboring *Escherichia coli* carriage

Variables	Subject 1	Subject 2	Subject 3
Demographic data			
Age (years)	49	66	45
Gender	male	male	male
Occupation in health care setting	-	-	-
Diet habit			
Boiled water use	-	+	+
Vegetarian	-	-	-
Daily animal contact	-	-	-
Travel abroad in the past 12 months	China	-	-
Medical history			
Antibiotic treatment in the past 3 months	-	-	-
Probiotics use in the past 3 months	+	-	+
Hypertension	-	-	-
Hyperlipidemia	-	-	-
Diabetes mellitus	-	-	-
Stroke	-	-	-
Gout or hyperuricemia	-	-	-
Renal function impairment	-	-	-
Chronic hepatitis B virus infection	-	-	+
Chronic hepatitis C virus infection	-	-	-
Colonic polyps	-	+	-
Cancer	-	-	-
MIC of colistin (mg/L)	2	2	4
Sequence type	ST2522	ST398	ST453

one participant with *mcr-1 E. coli* carriage remains undefined. Most *mcr-1*-harboring *E. coli* isolates were non-wild types, but some wild types were reported.^{31,32} The genetic relationship between our colonized isolates and the previously published isolates causing bloodstream infections or those obtained from pigs in Taiwan¹⁵ warrants further investigation.

In contrast to the prevalence data in China (4.9%)³³ and Hong Kong (2.1%),³⁴ fecal *mcr-1 E. coli* carriage in our adults visiting a health examination center was less common (0.4%), which was similar to results from The Netherlands (0.35%).³² The above data suggest geographic diversity of *mcr-1 E. coli* fecal carriage throughout the world and that *mcr-1 E. coli* is not widely spread in the community in Taiwan.

There are some limitations to this study. First, the participants only involved urban adults who received health examinations in one city, and the representativeness of the study cohort for the Taiwan population is limited. Second, the number of patients with ESBL-EC and ST131 *E. coli* carriage was too small to detect certain risk factors. Last, the association of colonic polyps and ESBL-EC may be biased because of recall bias for the diagnosis of colonic polyps. A prospective study enrolling individuals with colonic polyps that were diagnosed by colonoscopy and microbiological screening of fecal ESBL-EC carriage is warranted.

Conclusion

Asymptomatic adults in Taiwan had a low prevalence rate of fecal ESBL-EC or ST131 *E. coli* carriage, which was associated with the presence of underlying medical conditions. However, only a small number of ESBL-EC and ST131 *E. coli* isolates were noted in the study, and the associated risk factors require further investigation.

Ethics approval and informed consent

The study was approved by the Ethics Committee at the Kaohsiung Veterans General Hospital (VGHKS16-CT2-04). This study was conducted in accordance with the Declaration of Helsinki. The Ethics committee waived the need for written informed consent provided by participants due to the noninterventional and retrospective nature of the study. Because all patient data were analyzed in anonymity, no additional informed consent was required.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there are no competing interests regarding the publication of this paper.

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