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The change of antibiotic susceptibility in febrile urinary tract infection in childhood and adolescence during the last decade

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Purpose: The purpose of this study was to clarify the pattern of antibiotic resistance in pediatric urinary tract infections (UTIs).
Materials and Methods: We analyzed the data of entire urine culture tests and antibiotic susceptibility tests performed on hospitalized patients for febrile UTI at the Uijeongbu St. Mary's Hospital during 2010–2020. A retrospective analysis was performed using medical records of urine culture results and antibiotic susceptibility results in patients with UTIs.
Results: We performed urine cultures from 2,491 patients, and identified bacterial types in 1,651 cases. We found that the resistance rates to ampicillin, ampicillin/sulbactam, cefazolin, gentamicin, piperacillin, tobramycin, and trimethoprim/sulfamethoxazole were already over 20% in 2010. The resistance rates to many other antibiotics also steadily increased over time. Among the antibiotics tested in 2020, only amikacin, cefoxitin, imipenem, piperacillin/tazobactam, and tigecycline showed the resistance rates below 20%. Noticeably, ciprofloxacin also showed an increase in the resistance rate from 7.3% in 2010 (S 139 vs. R 11) to 27.78% in 2019 (S 104 vs. R 40) and even over 30% (33.96%) in 2020 (S 35 vs. R 18).
Conclusions: Antibiotic resistance is a serious problem in pediatric UTIs. In the treatment of pediatric UTIs, more caution is needed in the use of antibiotics. It may be necessary to apply appropriate antibiotic management programs such as antibiotics steward program for pediatric patients. Failure of a proper response strategy coping with antibiotic resistance may accelerate the resistance crisis.

Keywords: Antibiotic resistance; Antibiotics; Ciprofloxacin; Urinary tract infections

INTRODUCTION

Febrile urinary tract infection (UTI) is one of the most common conditions in febrile illness in infants and children [1]. In addition, 30% of newborns with urinary tract malformations may have a UTI as the first sign or symptom of abnormality [2]. UTIs in children, if not properly treated, may cause a variety of severe consequences of recurrent UTI and subsequent hospitalization, permanent decline in renal function due to the formation of inflammatory scars in the pediatric kidney in pyelonephritis, sepsis or bacteremia due to severe infection, and death. In addition to such clinical

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consequences, it may also lead to antibiotic resistance. In general, according to the clinical guidelines of the American Academy of Pediatrics, the diagnostic criteria for UTI are positive dipstick test, pyuria or bacteriuria in microscopic examination, and 50,000 cfu/mL pathogens in clean voided urine or suprapubic aspirated specimen.

For pediatric patients, prophylactic antibiotics, which prevent renal damage [3], are used to treat the diseases such as vesicoureteral reflux, ureteropelvic junction obstruction, primary megaureter, and ureterocele. UTIs accompanied by fever and leukocytosis, in particular, require patients to be hospitalized and treated with therapeutic antibiotics. A patient treated with antibiotics at an early stage may experience various adverse events at later times [4,5]. Recent studies have shown that the early exposure to antibiotics may alarm microbiota, and cause dysbiosis [6] and antibiotic resistance [7]. Therefore, exposure to antibiotics at a relatively early age and for a long period of time enhances the likelihood of developing antibiotic resistance.

While the emergence of expended-spectrum beta-lactamase positive pathogens as well as carbapenem-resistant pathogens has been already a serious problem in adult UTIs [8], the similar antibiotic resistance is also being raised as a clinical challenge in pediatric UTIs [9]. Antibiotic resistance has become a global problem beyond the national level. In this regard, long-term studies on antibiotic resistance in pediatric UTIs in Korea are urgent.

In this study, in order to further understand the recent situation of antibiotic resistance for UTIs, we have investigated the pattern of antibiotic resistance in pediatric UTI patients.

MATERIALS AND METHODS

Institutional ethics review was sought and the study was approved by the Catholic University of Korea, Institutional Review Board (approval number: UC16RCMI0120). Because only medical records were used, informed consent was not obtained. We analyzed the entire urine culture tests and antibiotic susceptibility tests performed on patients who received inpatient treatment for febrile UTI at the pediatric department of the Uijeongbu St. Mary's Hospital during the past decade (1 January, 2010–31 December, 2020). A retrospective analysis was performed using medical records of urine culture data and accompanying antibiotic susceptibility data in patients who had been diagnosed with UTIs such as UTI, cystitis, and acute pyelonephritis (APN) as the primary or secondary diagnosis. Based on the patient's urine culture results, the causative strains of infected pathogens were identified and the extended-spectrum beta-lactamase (ESBL) positivity and antibiotic susceptibility data were analyzed every year during the period of this study.

In the antibiotic susceptibility test, the tested antibiotics were not the same every year. However, if the antibiotics administered at the time of the examination were confirmed, they were compared. In this study, pathogens being defined to be intermediate and resistance in the susceptibility test were classified as antibiotic-resistant strains. Antibiotics studied were amikacin, ampicillin, ampicillin/sulbactam, aztreonam, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, cefuroxime, ciprofloxacin, colistin, doripenem, gentamicin, imipenem, levofloxacin, meropenem, piperacillin, piperacillin/tazobactam, ticarcillin/clavulanic acid, tigecycline, tobramycin, and trimethoprim/sulfamethoxazole. Regarding to the resistance rate, antibiotic resistance rate under 20% was set as the green zone, 20%–30% as the yellow zone, and the ratio over 30% as the red zone.

Urine culture for antimicrobial susceptibility test was performed by MicroScan (Beckman Coulter, Brea, CA, USA), VITEK2 (BioMerieux, Marcy-l'Etoile, France), and Microflex LT (Bruker Daltonics, Bremen, Germany).

RESULTS

1. General characteristics of pediatric urinary tract infection patients

A total of 2,498 pediatric patients including 1,141 males and 1,357 females were hospitalized for UTI, indicating that the male to female ratio was 1:1.19. The average number of UTI occurrence episodes was found to be significantly higher in female with 1.1 vs. 1.13 episodes (p=0.014). The primary diagnosis indicated APN (1,001 cases), UTI (847 cases), and acute cystitis (358 cases), and various other accompanying diseases could be identified. For imaging tests, KUB ultrasonography was performed in 2,153 patients and dimercaptosuccinic acid (DMSA) scan was performed in 1,581 cases. The general characteristics of pediatric febrile UTI patients are shown in Table 1.

To identify the infected bacterial strains, we tested 2,498 patients, and performed the urine cultures from 2,491 patients (Table 2). Among the 2,491 cases, bacteria were identified in 1,651 cases, while other 225 cases showed contamination. Among the total of 1,651 bacterial identification, *Escherichia coli* was found the most at 74.2%, non-specific strains including gram-positive cocci (GPC) accounted for the second most at 9.6%, and *Enterococcus faecalis* was the third at 6.8%. The distribution of the identified bacterial strains is shown in Fig. 1. Our results revealed that there were 126

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Table 1. The characteristics of pediatric febrile UTI patients during 2010–2020

Variable	Value
Number of patients	2,498
Number of pathogen	2,627
Sex	
Male	
ESBL(-)	650
ESBL(+)	122
Female	
ESBL(-)	487
ESBL(+)	103
Diagnosis	
Primary	
Acute cystitis	358
APN	1,001
FUO	42
UTI	847
GI disease	38
Hydronephrosis	3
Neurologic disorder	12
Pyuria	16
Renal disease	21
Respiratory disease	33
Sepsis	8
URI	83
Viral infection	15
VUR	6
Secondary	
Acute cystitis	202
APN	262
FUO	1
UTI	214
GI disease	65
Hydronephrosis	7
Neurologic disorder	26
Pyuria	47
Renal disease	5
Respiratory disease	19
Sepsis	17
URI	124
Viral infection	0
VUR	37
Ultrasonography findings	
Total	2,153
Normal	1,302
Hydronephrosis	128
Acute pyelonephritis	182
Pelviectasis	301
Cystitis	215
Others	25
DMSA findings	
Total	1,581
Cortical defect (-)	299
Cortical defect (+)	1,282

Values are presented as number only.
UTI, urinary tract infection; ESBL, extended-spectrum beta-lactamase; APN, acute pyelonephritis; FUO, fever of unknown origin; GI, gastrointestinal; URI, upper respiratory infection; VUR, vesicoureteral reflux; DMSA, dimercaptosuccinic acid.

cases with multiple types of pathogens: 122 cases with two types of strains, 3 cases with three types of bacteria, and 1 case with four types of bacteria.

2. Extended-spectrum beta-lactamase pathogens

The ESBL positivity test data demonstrated that 1,137 cases (83.5%) were ESBL(-) and 225 cases (16.5%) were ESBL(+). Intriguingly, ESBL(+) cases were gradually increased from 5.3% in 2010 to 9.2% in 2013, and almost doubled between 2013 and 2014 (Fig. 2).

3. Antibiotic susceptibility tests

During 2010–2020, we investigated the susceptibility to 23 antibiotics. Of note, there was a limitation in the continuous observation of certain antibiotics because the list of the antibiotics to be tested for antibiotic susceptibility was different every year. We compared the susceptibility to all antibiotics tested during 2010–2020, and observed a change of antibiotic susceptibility patterns.

In a 2010 survey, ampicillin, ampicillin/sulbactam, cefazolin, gentamicin, piperacillin, tobramycin, trimethoprim/sulfamethoxazole had already shown a resistance rate of over 20%. Most of other antibiotics also showed a steady increase in the resistance over time. Only amikacin, cefoxitin, imipenem, piperacillin/tazobactam, and tigecycline showed the resistance rate below 20% in 2020. Although it is restrictedly used for pediatric patients, ciprofloxacin also showed an increase in its resistance rate from 7.3% in 2010 (S 139 vs. R 11) to 27.78% in 2019 (S 104 vs. R 40) and 33.96% in 2020 (S 35 vs. R 18). In the case of ampicillin, ampicillin/sulbactam, and piperacillin, the resistance rates of those antibiotics consistently showed more than 60% during the past 10 years of this study. During the period of this study, amikacin and carbapenems, including imipenem, doripenem, and meropenem, kept less than 10%, while cefoxitin kept less than 20% in most years tested in our study. Aztreonam, cefepime, ticarcillin/clavulanic acid, and trimethoprim/sulfamethoxa-

Table 2. The uropathogen patterns in pediatric febrile UTIs during 2010–2020

Variable	Year										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Number of patients	222	226	208	244	267	200	254	322	250	232	73
Male	110	97	119	112	140	96	109	128	86	101	43
Female	112	129	89	132	127	104	145	194	164	131	30
Pathogen											
Escherichia coli	110	106	119	115	117	110	124	145	112	120	47
Klebsiella pneumoniae	11	9	6	6	21	3	7	13	3	10	3
Klebsiella oxytoca	1	4	0	1	1	1	2	4	2	4	2
Pseudomonas aeruginosa	1	0	1	2	1	4	3	0	0	0	0
Proteus mirabilis	5	3	2	2	4	1	3	3	0	1	0
Enterococcus faecalis	8	8	11	7	12	6	7	13	23	15	3
Enterococcus faecium	2	6	6	9	6	2	2	2	7	0	0
Other (GPC and etc.)	13	12	17	26	16	13	11	5	26	19	0

Values are presented as number only.
UTI, urinary tract infection; GPC, gram-positive cocci.

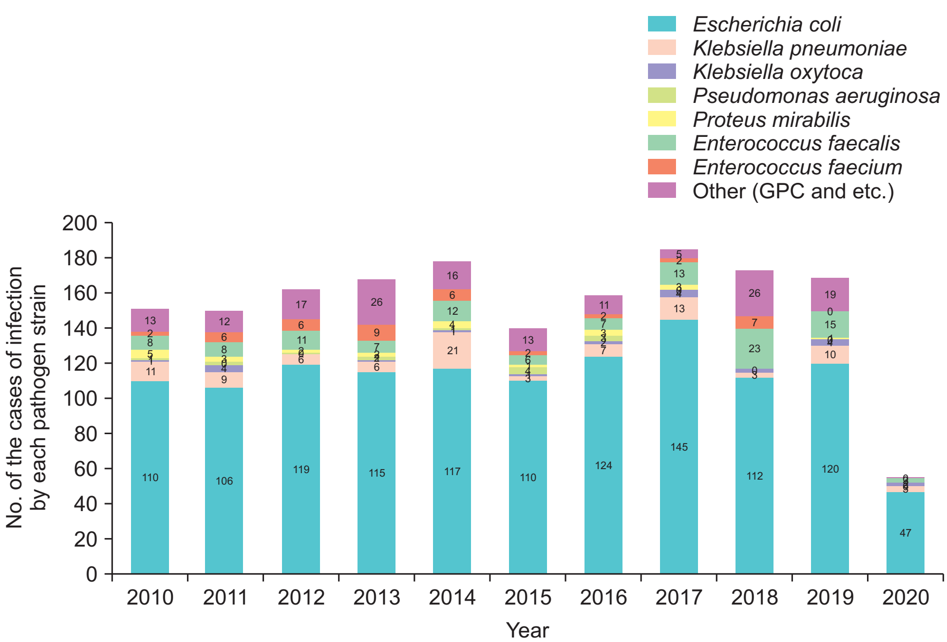

Fig. 1. Annual numbers of the cases of infection caused by each pathogen in pediatric UTI patients. Urine cultures derived from pediatric patients who received inpatient treatment for febrile UTI during 2010–2020 were examined for the identification of pathogenic bacteria, as described in the MATERIALS AND METHODS. UTI, urinary tract infection; GPC, gram-positive cocci.

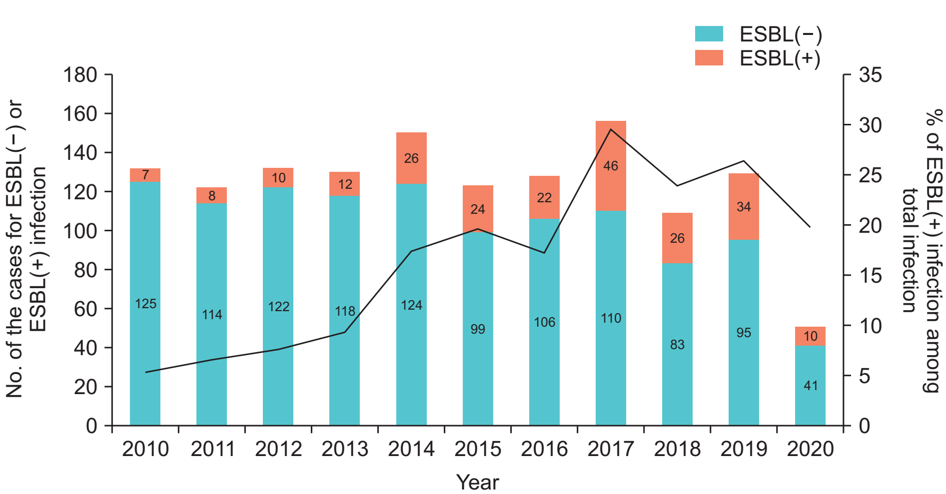

Fig. 2. Annual numbers of the cases of ESBL-negative or ESBL-positive infection. Urine cultures derived from pediatric patients who received inpatient treatment for febrile UTI during 2010–2020 were examined by ESBL test. The testing data were quantified for ESBL-negative (blue) or ESBL-positive (orange) infection. The percentages of the ESBL-positive infection among total infection were also shown (black line). ESBL, extended-spectrum beta-lactamase; UTI, urinary tract infection.

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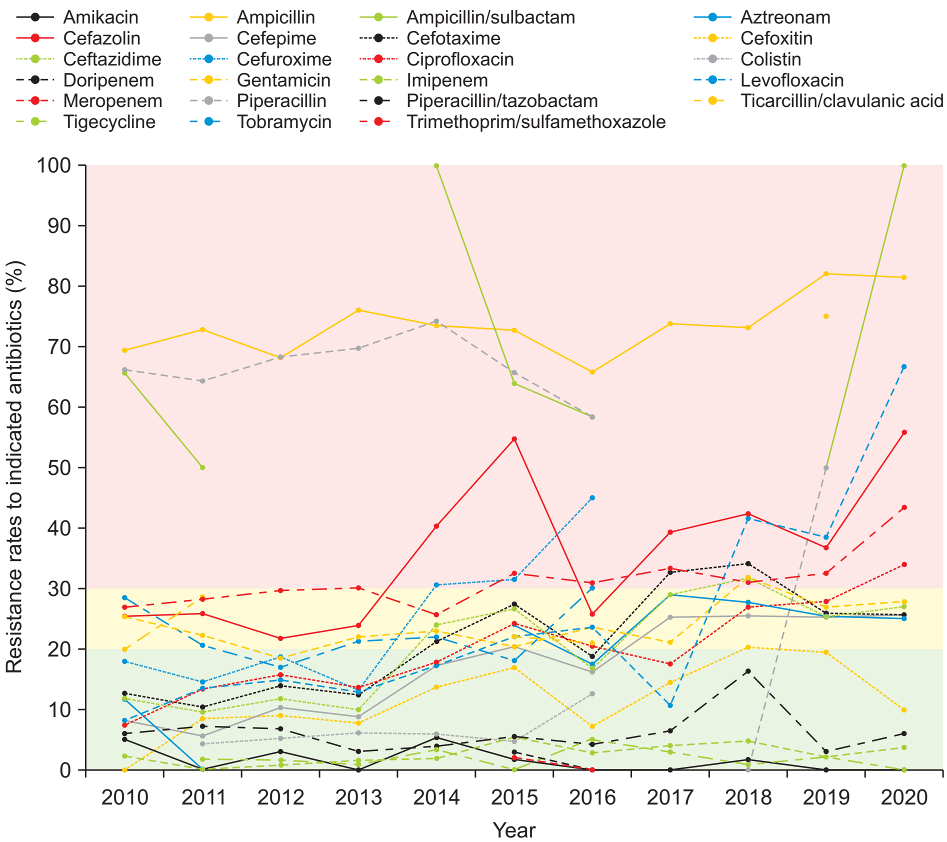

Fig. 3. Annual changes of the resistance rates to indicated antibiotics. Urine cultures derived from pediatric patients who received inpatient treatment for febrile UTI during 2010–2020 were examined by antibiotic resistance test. The resistance rates to indicated antibiotics were analyzed, and grouped into 3 zones (red, over 30 %; yellow, 20%–30%; green, less than 20%). UTI, urinary tract infection.

zole might have been considered as selectable and available antibiotic options in 2010; however, they showed a high resistance rate in 2020 (Fig. 3).

Given the antibiotic resistance rates in the green/yellow/red zones shown in Fig. 3, there were 12 antibiotics in the green zone and 3 antibiotics in the red zone in 2010. In comparison, in 2020 there were only 5 antibiotics in the green zone. The numbers of available antibiotics with relatively low antibiotic resistance dramatically decreased during the last decade.

DISCUSSION

Pediatric UTI is a disease with a prevalence of about 7%, which shows some variations according to gender and age [10]. Although only few studies on pediatric UTI have been reported in Korea, a recent domestic study suggests that pediatric UTIs in children younger than 1 year are more common in boys, whereas those in children older than 1 year are more in girls [11].

Infections cause not only medical problems but also various social and economic problems worldwide. In recent years, the continued use of antibiotics has brought serious problems in various ways, including dysbiosis resulting from the antibiotics-induced breakdown of microbiota homeostasis, which can also cause other diseases [12]. Furthermore, antibiotic resistance is one of the most common problems experienced and encountered in clinical practice. With generating a number of clinical problems in the treatment of infectious diseases, an increase in antibiotic resistance narrows the position of antibiotics as a therapeutic strategy against infectious diseases [13].

In adult patients, infections caused by ESBL-positive pathogens have already brought various problems in the therapeutic use of antibiotics in the medical field, given that the causative microorganisms of the first infection may acquire antibiotic resistance. In particular, Asia is a major region exhibiting high levels of resistance to quinolone in adults [13]. Korea is classified as a country with high antibiotic resistance, with being considered to reach a seriously high level of quinolone resistance. It is difficult to use quinolone for practical application to pediatric patients. We, however, have found in this study that the resistance rates of other antibiotics have already reached serious levels. Furthermore, the resistance rates of ESBL-positive pathogens are also increasing significantly.

Pediatric UTIs are often associated with urinary tract malformations. If these malformations are not severe, prophylactic antibiotics are administered to prevent the renal parenchymal damage caused by UTI [1,7,14]. The therapeutic and preventive goal of the treatment of UTI in children is to reduce morbidity and mortality as well as to prevent renal scarring [15]. It has been suggested that certain factors such as age, gender, race, and circumcision status in males affect resistance and clinical features in pediatric UTI [10]. In one study, clinical features associated with relapse in UTI caused by ESBL-positive pathogens did not show a significant difference from those of ESBL-negative pathogens, implicating that general antibiotics should be used for the treatment of pediatric UTI [16].

Foreign studies on *E. coli*, one of the main causative bacteria of UTI in children, showed somewhat different results from this study. European studies have reported that the third-generation cephalosporin would be more effective because of the high levels of ampicillin resistance across European countries [17]. In comparison, in the studies in North America, amoxicillin as well as the second- or third-generation cephalosporins have been suggested as drugs of choice [1]. Thus, recommendations for antibiotics vary from region to region, depending on the antibiotic resistance rates and available antibiotics. Although other antibiotics can still be used clinically, amikacin and piperacillin/tazobactam showed superior sensitivity in this study if the antibiotic resistance rates are taken into account even though they have hepatotoxicity and nephrotoxicity. In case of antimicrobial therapy for infections caused by ESBL-positive pathogens, amikacin, and piperacillin/tazobactam may be considered first to minimize the use of carbapenem.

We have shown in this study that the percentages of ESBL-positive pathogens in children, newborns, and adolescents increased every year. Moreover, the resistance rates of the antibiotics belonging to the broad-spectrum antibiotic class have rapidly increased, while the antibiotics applied to the antibiotic stewardship program have maintained sensitivity. These findings are in good agreement with previous foreign studies suggesting that urologists are needed to be cautious to use drugs because of an increase in antibiotic resistance [7]. It is also noteworthy that there is a meta-analysis study suggesting a careful use of antibiotics for the treatment of pediatric UTI in primary medical institutions [18].

One of the emerging problems in pediatric patients is the infection of carbapenem-resistant pathogens [19], as in adults. In adult patients, carbapenem resistance, with already being spread rapidly, has been a major public health problem globally [20,21]. In fact, various attempts have been made to prevent the emergence of carbapenem-resistant pathogens. One study has implicated aminoglycoside as an alternative to carbapenem in the antibiotic therapy for children infected with ESBL-positive pathogens [22], while other studies have suggested the effectiveness of piperacillin/tazobactam [23], or ceftazidime-avibactam in a phase 3 RECAPTURE program [24]. Thus, diverse efforts are made for minimizing the use of carbapenem or the use of it along with other antibiotic classes. Our results in this study revealed that amikacin consistently exhibits less than 10% antibiotic resistance, suggesting that it might be used for retarding the emergence of CRE strains and for restricting the use of carbapenem in the treatment of pediatric UTI.

There are some caveats regarding our findings in this study. Firstly, this study was carried out with the patients from a single institution; therefore, our data in this study would not be representative of the national values of antibiotic sensitivity and resistance rate in Korea. In this respect, it is urgently needed to conduct nationwide and multicenter studies on the antibiotic susceptibility and resistance in Korea. Secondly, our study is a retrospective study, therefore, it is difficult to clarify the correlation between antibiotic sensitivity and actual clinical features. Future studies analyzing the characteristics as well as antibiotic efficacy and susceptibility of ESBL-positive strains would shed more insight into the better treatment of pediatric UTIs. Given that a variety of UTIs in children may cause various sequelae including deterioration of renal function, it is necessary to establish well-planned strategy for conducting long-term and systematic clinical research for pediatric UTI and its related fields.

CONCLUSIONS

Antibiotic resistance in pediatric UTI is under a serious status, with its rate rising steeply. In pediatric UTIs, therefore, more caution is needed in the therapeutic use of antibiotics. It may be necessary to apply appropriate antibiotic control and management programs such as antibiotics steward program for pediatric patients. Failure of a proper response strategy coping with antibiotic resistance may accelerate the resistance crisis, which might be predicted to come in the not-too-distant future.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Useok Choi, Kang Seob Kim, Bong Hee Park, Hong Chung, Chang Hee Han, and Sangrak Bae. Data acquisition: Useok Choi, Eunjae Kim, and Don Hee Lyu. Statistical analysis: Useok Choi and Sangrak Bae. Data analysis and interpretation: Useok Choi and Sangrak Bae. Drafting of the manuscript: Useok Choi. Critical revision of the manuscript: Useok Choi. Obtaining funding: Sangrak Bae. Administrative, technical, or material support: Kang Seob Kim, Bong Hee Park, Hong Chung, Chang Hee Han, and Sangrak Bae. Supervision: Sangrak Bae. Approval of the final manuscript: Sangrak Bae.

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