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Microbial etiology and antibiotic resistance in urinary tract infections in children; view from an area where antibiotics are overused

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Abstract. – OBJECTIVE: The aim of our study is to determine the uropathogenic causing urinary tract infections (UTIs) and their incidences, assess their antibiotic resistance, and determine an appropriate empirical antibiotic treatment strategy.

PATIENTS AND METHODS: We retrospectively analyzed the culture and antibiogram results of urine cultures of 49,706 patients aged 1 day to 18 years who applied to Diyarbakır Children's Hospital between March 2018 and October 2022.

RESULTS: A total of 4,064 cases meeting the study criteria were recorded. Girls comprised 76.7% of the study population. While reproduction in urine culture was more common in boys in the 0-1 age group, there was a decrease in the number of boys with increasing age, and the most common culture growth was seen in girls in the 5-10 age group ($p<0.001$). *Escherichia coli (E. coli)* infections were more common in girls, while non-*E. coli* infections were more common in boys ($p<0.001$). Gram-negative bacterial growth in urine cultures was the most common growth type. In descending order, *E. coli* was grown in 68.1% of all cultures, *Klebsiella spp* in 12.6%, and *Proteus spp* in 3.9%. Less commonly, *Pseudomonas spp* (2.8%), *Enterobacter spp* (1.5%), and fungi (1.1%) were grown. Antibiotic resistance/sensitivity tests revealed resistance patterns most commonly against ampicillin (73.2%), amoxicillin-clavulanate (57.9%), cefuroxime axetil (46.7%), cefixime (51%), and ceftriaxone (40.5%), and less commonly against meropenem (1.7%), amikacin (2.4%), and nitrofurantoin (9.8%). *Escherichia coli* showed resistance most commonly against ampicillin (69.8%), amoxicillin-clavulanate (59.7%), and cefixime (51.3%), while non-*E.coli* bacteria showed resistance most commonly against ampicillin (84.6%), amoxicillin (52.0%), and cefixime (50%). Resistance against nitrofurantoin was lower in *E. coli* infections than non-*E. coli* infections, although the difference did not reach statistical significance (3.7% and 27%, respectively; $p=0.149$). In contrast, resistance against trimethoprim-sulfamethoxazole was more common in *E. coli* infections than non-*E. coli* infections, although the difference was not statistically significant (42% and 29.7%, respectively; $p=0.093$).

CONCLUSIONS: Our study revealed that resistance has developed at very high rates against many oral and parenteral antibiotics that we use in the treatment of UTIs. If our rate of antibiotic use continues to increase this way, it is predicted that UTIs will, unfortunately, become untreatable with oral antibiotics. This upsetting point reached by our country, which is the state that uses antibiotics the most in Europe, exemplifies the importance of rational antibiotic use for the whole world.

Key Words:
Antibiotic resistance, Urinary tract infection, Child.

Introduction

Urinary tract infection (UTI) is the most common bacterial infection seen in children. It is defined as bacterial proliferation in the urinary system and may present with acute cystitis, acute pyelonephritis, or asymptomatic bacteriuria[1]. In children, conditions such as congenital anomalies of the urinary tract (ureteropelvic junction obstruction, posterior urethral valve, vesicoureteral reflux, neurogenic bladder, etc.), clean intermittent catheterization, and voiding disorders create a predisposition to UTIs[2]. Urinary tract infections are important because they lead to renal scarring, hypertension, and end-stage renal failure[1]. The incidence of febrile UTIs is 7.0% for children aged 0-24 months and 7.8% for older children. The incidence in boys is considerably high in the first three months and then rapidly drops[3]. By the age

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of 7 years, 8.4% of girls and 1.7% of boys will have had one or more symptomatic UTI episodes[1]. *Escherichia coli* (*E. coli*) is the pathogen responsible for 68-90% of all UTIs. Apart from *E. coli*, many pathogens, such as *Klebsiella spp*, *Proteus spp*, and *Enterococci* can cause UTI[4]. Because it takes time for urine culture results to come out, empirical treatment has an important role in the treatment of UTIs. Cefixime/cefalexin, trimethoprim/sulfamethoxazole (TMP-SMX), and amoxicillin-clavulanic acid are the preferred empirical treatment choices for children with fever who can take oral medication[1]. Inappropriate antibiotic selection may lead to treatment failure and an increased rate of bacterial resistance. This may result in irreversible disorders such as renal parenchymal injury, renal dysfunction, renal hypertension, and chronic kidney disease[5]. Since antibiotic resistance patterns may change over time, they must be continuously monitored in a region, country, and world. The aim of our study is to determine the uropathogens causing UTIs and their incidences, assess their antibiotic resistance, and determine an appropriate empirical antibiotic treatment strategy.

Patients and Methods

We retrospectively examined the urine culture and antibiogram of patients aged 1 day to 18 years who presented to Diyarbakır Pediatric Hospital between March 2018 and October 2022. The inclusion criterion was determined as having growth of only one strain of microorganism with a colony count $>10^5$ CFU/mL in urine culture. Since there are no clinical data about the use of clean intermittent catheterization and samples collected with the urethral catheter or suprapubic aspiration, bacterial growth of $>10^5$ CFU/mL in urine samples obtained by all methods was considered significant for UTI. Samples considered to be contaminated were excluded. The patients' demographic characteristics, outpatient/inpatient status, strains grown in urine cultures, and antibiotic resistance/sensitivity were recorded. Since the patients' clinical data (fever, nausea-vomiting, dysuria, etc.) were missing, differential diagnoses such as pyelonephritis, cystitis, and asymptomatic bacteriuria could not be made.

In our center, urine culture samples are examined by a microbiologist after they are inoculated on 5% sheep blood 'agar and eosin methylene blue' medium and kept at 37°C under aerobic conditions for 24-48 hours. Antibiotic sensitivity of bacteria grown in cultures is tested by conventional methods and VITEK 2 Compact (bio Mérieux, Marcyl' Etoile, France) system. Sensitivity tests for ampicillin, amoxicillin-clavulanate, amikacin, cefixime, cefuroxime-axetil, ceftriaxone, ciprofloxacin, meropenem, trimethoprim/sulfamethoxazole, and nitrofurantoin are carried out using the disk diffusion method in line with the recommendations of European Committee on Antimicrobial Susceptibility Testing (EUCAST)[6].

Ethics

The procedures were in accordance with the ethical standard for human experimentation established by the Declaration of Helsinki 1975, as revised in 2013. The study was approved by the Ethics Committee of Diyarbakır Gazi Yaşargil Training and Research Hospital (Ethical Committee No. 236/2022).

Statistical Analysis

The normality of data distribution was checked with histograms and Kolmogorov-Smirnov test. The Chi-square test was used to compare categorical variables. Bacterial pathogens were divided into two groups: *E. coli* and non-*E. coli,* and statistical analyses were performed accordingly. Statistical significance was set at p-value <0.05. Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Urine cultures were sent from 49,706 patients who presented to Diyarbakır Pediatric Hospital between March 2018 and October 2022. Among them, 4,517 patients had bacterial growth in urine culture. A total of 4,064 cases meeting the inclusion criteria were enrolled. Girls made up 76.7% of the study population. While growth in urine cultures was more common in boys in the 0-1 age group, the number of boys decreased as age increased, and the most common culture growth occurred in girls aged 5-10 years (Table I) ($p<0.001$). Whereas non-*E. coli* infections were more common in the first 2 years of age, *E. coli* infections were more common in older patients (Table I) ($p<0.001$). *E. coli* infections were more common in girls, whereas non-*E. coli* infections were more common in boys (Table II) ($p<0.001$).

Table I. Distribution of patients with growth in urine culture by age and gender.

	0-1 month n (%)	1-24 month n (%)	2-5 years n (%)	5-10 years n (%)	>10 years n (%)	Total n (%)
Gender*						
Female	44 (38.9)	528 (56)	656 (84.8)	1,179 (90.4)	710 (76.3)	3,117 (76.7)
Male	69 (61.1)	415 (44)	118 (15.2)	125 (13.2)	220 (23.7)	947 (23.3)
Total	113	943	774	1304	930	4,064
Microorganism**						
E. coli	50 (44.2)	431 (45.7)	560 (72.4)	1,099 (84.3)	628 (67.5)	2,768 (68.1)
Non-*E. coli*	62 (54.9)	502 (53.2)	199 (25.7)	199 (15.3)	291 (31.3)	1,253 (30.8)
Fungal	1 (0.9)	10 (1.1)	15 (1.9)	6 (0.5)	11 (1.2)	43 (1.1)
Total	113 (100)	943 (100)	774 (100)	1,304 (100)	930 (100)	4,064 (100)

*p-value was <0.001 when comparing age groups and genders with the Chi-square test. **p-value was <0.001 when comparing age groups and microorganism groups with the Chi-square test.

Table II. Microorganisms reproduced according to the sex of the patients.

	Female [n (%)]	Male [n (%)]	Total	p-value*
E. coli	2,394 (76.8)	374 (39.5)	2,768 (68.1)	<0.001
Non-*E. coli*	698 (22.4)	555 (58.6)	1,253 (30.8)	
Fungal	25 (0.8)	18 (1.9)	43 (1.1)	
Total	3,117 (100)	947 (100)	4,064 (100)	

*Comparing microorganism groups and genders with the Chi-square test.

Outpatients constituted 64.4% of the study population. *Escherichia coli* infection was more common in both inpatients and outpatients (Table III) (p<0.001).

Gram-negative bacterial growth in urine cultures was the most common growth type. In descending order, *E. coli* was grown in 68.1% of all cultures, *Klebsiella spp* in 12.6%, and *Proteus spp* in 3.9%. Less commonly, *Pseudomonas spp* (2.8%), *Enterobacter spp* (1.5%), and fungi (1.1%) were grown. The rates of microorganisms by year are shown in Table IV. Antibiotic resistance/sensitivity tests revealed resistance patterns most commonly against ampicillin (73.2%), amoxicillin-clavulanate (57.9%), cefuroxime axetil (46.7%), cefixime (51%), and ceftriaxone (40.5%), and less commonly against nitrofurantoin (9.8%), amikacin (2.4%), and meropenem (1.7%). A comparison of yearly antibiotic resistance rates over a 5-year period between *E. coli* and non-*E. coli* infections by the Chi-square test showed that the rates of resistance against antibiotics other than meropenem and amikacin did not change significantly. Table V shows the rates of antibiotic resistance by year.

Escherichia coli showed resistance most commonly against ampicillin (69.8%), amoxicillin-clavulanate (59.7%), and cefixime (51.3%), while non-*E. coli* bacteria showed resistance most commonly against ampicillin (84.6%), amoxicillin (52.0%), and cefixime (50%) (Table V). Resistance against nitrofurantoin was lower in *E. coli* infections than non-*E. coli* infections, although the difference did not reach statistical signifi-

Table III. Microorganisms detected in outpatients and inpatients.

	Outpatient	Inpatient	Total	p-value
E. coli	1,857 (45.7)	911 (22.4)	2,768 (68.1)	<0.001
Non-*E. coli*	758 (18.7)	495 (12.2)	1,253 (30.8)	
Fungal	3 (0.1)	40 (1.0)	43 (1.1)	
Total	2,618 (64.4)	1,446 (35.6)	4,064 (100)	

Table IV. Distribution of reproducing pathogens by years.

	2018	2019	2020	2021	2022	Total
E. coli	229 (65.4)	422 (69.1)	449 (66.8)	968 (68.2)	700 (69.2)	2,768 (68.1)
Klebsiella spp	41 (11.7)	72 (11.8)	76 (11.3)	173 (12.2)	152 (15)	514 (12.6)
Proteus spp	3 (1.9)	14 (2.3)	33 (4.9)	75 (5.3)	34 (3.4)	159 (3.9)
Pseudomonas spp	18 (5.1)	25 (4.1)	22 (3.3)	36 (2.5)	13 (1.3)	114 (2.8)
Enterobacter spp	6 (1.7)	10 (1.6)	10 (1.5)	20 (1.4)	13 (1.3)	59 (1.5)
Fungus	5 (1.4)	5 (0.8)	14 (2.1)	15 (1.1)	4 (0.4)	43 (1.1)
Others	48 (13.7)	63 (10.3)	68 (10.1)	133 (9.4)	95 (9.4)	407 (10)
Total	350	611	672	1,420	1,011	4,064

cance (3.7% and 27%, respectively; p=0.149). In contrast, resistance against TMP-SMX was more common in *E. coli* infections than non-*E. coli* infections, although the difference was not statistically significant (42% and 29.7%, respectively; p=0.093) (Table V).

Discussion

The discovery of antibiotics gave rise to great hopes in medicine. But unfortunately, resistance patterns to antibiotics are rising all over the world due to the high consumption of antibiotics in humans, animals and even in agriculture. For all these reasons, antibiotic resistance has now become a public health problem all over the world. Despite all national and international efforts to reduce antibiotic use, unnecessary antibiotic use cannot be prevented. Similar increasing trends in antibiotic resistance have been observed in many studies of children with UTIs[7-12]. Similarly, to the literature, *E. coli* was the most common pathogen in our study, although non-*E. coli* bacteria were more common in the first two years of life. Very high resistance rates were observed, particularly against ampicillin (73.2%) and amoxicillin-clavulanate (57.9%). Furthermore, it was observed that resistance rates were high against cephalosporins and TMP-SMX, that we frequently use for empirical treatment. It was found that nitrofurantoin is the only oral antibiotic with a resistance rate below 20% that we can use in children. The EAU/ESPU guidelines[13] have reported that the incidence of UTIs is 20.3% in uncircumcised male infants and 5% in girls in the first two months of life. Shaikh et al[14] reported that 91% of children with UTIs were female, and 49% were 2-11 years old. Our study showed that 76.7% of children with UTI were girls, and bacterial growth most commonly occurred between 5 and 10 years of age. Studies have named *E. coli*, a gram-negative bacterium, as the most common uropathogen, and more rarely *Klebsiella spp*, *Enterobacter spp*, and *Proteus spp*[15-17].

According to different sources in literature, *E. coli* infections have a rate ranging between 68% and 90%; Accordingly, a recent review by Tullus et al[18] reported 80-90%, Çoban et al[19] 68%, and a study from Lebanon 79.4%. In our study, the incidence of E. coli was found to be 68.1%. Although the incidence of E. coli-related UTI in children has been reported at different rates in different studies, it is still the most common UTI agent. This figure varies in different age groups. Non-*E. coli* infections may be more commonly seen in infants. Hanna-Wakim et al[20] reported an incidence of 60% for *E. coli* and 28.1% for *Klebsiella pneumonia* in the first two months of life, while Mohammed et al[21] reported that *E. coli* had an incidence of 52.1% and *Klebsiella* 34.1% in infants. In our study, non-*E. coli* infections were more common under the age of 2 years. In the first month of life, *E. coli* had an incidence of 44.2% and non-*E. coli* bacteria 54.9%; similarly, *E. coli* had an incidence of 45.7% and non-*E. coli* 53.2% between the first and twenty-fourth month of life.

Antibiotic resistance patterns may vary by country and region. High antibiotic resistance rates have been reported by studies conducted in the United States and Croatia[22,23]. According to the study[24] examining antibiotic use and antibiotic resistance rates in Turkey and European countries, Turkey was the country that consumes the most antibiotics in terms of daily defined dose antibiotic use (GTD) per thousand people between 2005 and 2015. Turkey is followed by Greece, Spain, and France, respectively. An analysis of the average antibiotic consumption of these countries between 2005 and 2015 and their antibiotic resistance rates in 2014 has shown that the countries with the highest antibiotic consumption mostly rank at the top of the antibiot-

Table V. Distribution of detected antibiotic resistance by years and microorganisms.

	2018 (%)	2019 (%)	2020 (%)	2021 (%)	2022 (%)	Total (%)	*p*-value*
Ampicillins							
E. coli	66.4	71.2	70.4	70.7	68.6	69.8	
Non-*E. coli*	84.0	82.2	81.5	84.8	88.4	84.6	0.689
Total	70.7	73.6	73.2	73.9	73.0	73.2	
Amoxicillin-clavulanate							
E. coli	75.3	80.9	54.7	56.2	54.0	59.7	
Non-*E. coli*	72.5	57.5	30.1	50.0	48.8	52.0	0.438
Total	74.6	75.7	53.6	54.7	52.8	57.9	
Amikacin							
E. coli	0	0.6	0.7	2.9	1.9	1.7	
Non-*E. coli*	3.3	8.0	4.8	5.8	1.4	4.5	0.004
Total	0.9	2.4	1.7	3.7	1.7	2.4	
Cefuroxime axetil							
E. coli	38.3	47.6	47.4	46.7	49.0	46.9	
Non-*E. coli*	47.9	50.6	46.2	47.5	40.9	45.8	0.698
Total	40.1	48.2	47.1	46.9	47.3	46.7	
Ceftriaxone							
E. coli	45.7	36.7	46.5	47.1	33.4	40.4	
Non-*E. coli*	25.0	40.0	47.3	49.3	32.3	40.8	0.408
Total	40.4	37.0	46.7	47.7	33.2	40.5	
Cefixime							
E. coli	53.5	63.3	49.3	52.0	45.8	51.3	
Non-*E. coli*	44.7	55.3	52.0	54.8	41.8	50.0	0.497
Total	51.3	61.6	49.8	52.7	44.8	51.0	
Trimethoprim/sulphametaxazol							
E. coli	48.1	58.6	38.9	42.3	34.6	42.0	
Non-*E. coli*	23.5	28.9	30.2	35.6	23.8	29.7	0.093
Total	39.9	49.9	36.4	40.3	31.4	38.3	
Nitrofurantoin							
E. coli	2.0	3.7	5.2	4.8	1.5	3.7	
Non-*E. coli*	29.8	14.8	33.8	35.8	16.8	27.0	0.149
Total	8.8	6.3	12.0	12.8	6.2	9.8	
Ciprofloxacin							
E. coli	21.0	24.5	16.3	18.4	14.3	17.8	
Non-*E. coli*	21.4	17.8	20.7	21.3	16.5	19.6	0.109
Total	21.1	22.6	17.7	19.4	14.9	18.3	
Meropenem							
E. coli	0.0	0.0	0.3	0.8	1.4	0.9	
Non-*E. coli*	0.9	3.8	3.8	3.3	1.8	4.0	0.001
Total	1.8	1.1	1.1	1.5	1.5	1.7	

ic resistance rankings. Greece ranks first, followed by Turkey in antibiotic resistance rate[24]. The resistance rates of antibiotics to be used in the empirical treatment of patients diagnosed with UTI should not exceed 20%[25]. Thus, the Society of American Infectious Diseases reported that it is essential to have a knowledge of regional UTI pathogens and their level of antibiotic resistance[26]. In this context, according to our regional data, empirical treatment options are limited to nitrofurantoin (9.8%), ciprofloxacin (18.3%), amikacin (2.4%), and meropenem (1.7%). However, ampicillin, amoxicillin/amoxicillin-clavulanate, TMP-SMX, and second/third generation cephalosporins are more commonly selected for empirical treatment[27]. Oral antibiotics are commonly prescribed due to their ease of use

in children[27]. Our study revealed that *E. coli*, which was the most commonly isolated uropathogens, showed a high rate of resistance to empirically prescribed ampicillin, amoxicillin-clavulanate, TMP-SMX, cefuroxime axetil, and cefixime. Domestic and foreign studies[22,23,28,29] have reported increased resistance rates against ampicillin and TMP-SMX. In 2019, Kalaitzidou et al[10] from Greece reported an ampicillin resistance rate of 41.8% for *E. coli*. Three large-scale studies[30,31] from our country reported ampicillin resistance rates of 82.1%, 68.9%, and 25.4% for *E. coli*. A comparative study[28] of year-by-year change of antibiotic resistance showed that *E. coli*'s resistance rate against ampicillin, TMP-SMX, and cefazoline increased considerably between 2019-2021 compared with 2013-2015[28]. When the data were compared with the study[27] conducted in the same region 5 years ago, we observed that *E. coli*'s resistance rate against ampicillin has increased by 8.6% over a 5-year period. Similarly, studies in various countries have reported high rates of amoxicillin clavulanate resistance. In a multicenter study in 16 pediatric nephrology centers from 10 European countries, 4,745 urine cultures were evaluated[32]. The results showed that amoxicillin resistance was above 50% among inpatients in 14 of 16 centers and above 50% among outpatients in 8 of 16 centers. Resistance rates varied between 21% and 50% in 6 of 16 centers. It was also reported that there was resistance against TMP-SMX in more than 21% of the uropathogens in all inpatients and outpatients in 8 centers[32]. In accordance with domestic and foreign literature, our study found a rate of resistance of 57.9% against amoxicillin. In a global meta-analysis[7], the rates of resistance against TMP-SMX in pediatric UTIs caused by *E. coli* in high-income countries and countries outside the Organization for Economic Co-operation and Development (OECD) were found to vary between 30.2% and 69.6%. Differences in rates of antibiotic resistance between the abovementioned studies may be interpreted as the effects of the socio-economic development level and the prevalence of antibiotic use in the countries on the resistance pattern. We believe that one should exercise more caution when using these antibiotics for empirical treatment and avoid using them as the first treatment choice. Studies[29,33] have reported resistance rates of 5.2% and 4.1% against nitrofurantoin; our study found a figure of 9.8%, which shows that this antibiotic still maintains its position as an option in empirical treatment. Resistance rates against third-generation cephalosporins, which are broadly used in pediatrics, have been rising all over the world. The use of these antibiotics as the first choice and their frequent preference in outpatients and inpatients are one of important reasons for increased resistance rates[17,34]. Our study found a rate of resistance of 40.5% against third-generation cephalosporins. A rate of 27.2% was reported in a study[29] on patients in the same category five years ago, and we noticed a significant increase in resistance rate in the five-year period. In a study by Bozkurt et al[29], the resistance rate against ceftriaxone was reported to be 24.4%. In a domestic study[35] dated 2021, an antibiogram result chart for UTIs caused by *E. coli* showed a rate of 63.7% for ceftriaxone resistance. In a recent review of the AAP guidelines, Mattoo et al[36] highlighted that a great majority of uropathogens were sensitive to third-generation cephalosporins; on the other hand, the authors made recommendations against the use of amoxicillin due to high rates of resistance. We believe this increase in resistance is related to a gradual increase in antibiotic use in our country.

An analysis of the parenteral antibiotic resistance rates in our study revealed rates of 2.4% and 1.7% for resistance against amikacin and meropenem, respectively, which agreed with domestic and foreign studies[37,38]. Compared with the studies[19] conducted with these antibiotics in previous years, resistance patterns were noted not to have changed dramatically. We are of the opinion that amikacin from the aminoglycoside group can be used with care due to its nephrotoxicity and ototoxicity. Although the rate of resistance against meropenem, a broad-spectrum carbapenem, was found to be low, it should not be selected as the first choice in empirical treatment. According to our results, we detected rates of resistance exceeding 20% against widely used medications such as ampicillin, amoxicillin-clavulanate, TMP-SMX, ceftriaxone, cefixime, cefuroxime axetil whereas resistance against amikacin, nitrofurantoin, and meropenem was low.

Nitrofurantoins are considered an alternative choice in empirical treatment due to their high passage to the urinary system, urinary excretion, and low rate of resistance.

Although our study was a retrospective study, we lacked patients' history and clinical findings, and we had limited information about certain clinical data such as their comorbidities and history of antibiotic use, this study is important in showing antibiotic resistance in our country, particularly our region, because of its large population size.

Antibiotic resistance has been growing as a global issue worldwide, and analyses have shown that similar increase trends have occurred in

countries where antibiotic consumption is high. This highlights the importance of rational antibiotic use. While forming the health policies of the countries and planning the treatment of urinary tract infections, it is essential to act according to the uropathogens grown in microbiological cultures and their sensitivity level in the antibiogram, and the regional resistance pattern should be taken into consideration.

We are of the opinion that treatment planning should be done by giving consideration to regional differences as this issue may cause significant problems all over the world.

Conclusions

In conclusion, our study revealed that resistance has developed at very high rates against many oral and parenteral antibiotics that we use to treat UTIs. If our rate of antibiotic use continues to increase, it is predicted that UTIs will, unfortunately, become untreatable with oral antibiotics. The current situation in our country is concerning as we are the highest consumer of antibiotics in Europe. This highlights the significance of using antibiotics in a rational manner, not only for our country but for the entire world.

Authors' Contributions

Study concept and design, S.S., A.S.P.; acquisition of data, S. S. and A.S.P.; analysis and interpretation of data: A.S.P.; drafting of the manuscript, S.S.; critical revision of the manuscript for important intellectual content, A.S.P.; statistical analysis, A.S.P.; administrative, technical, and material support, S.S.; study supervision, A.S.P.

Conflict of Interest

The authors claimed no conflict of interest.

Ethics Approval

This study was approved by the Ethics Committee of SBU Diyarbakir Gazi Yaşargil Training and Research Hospital Ethics Committee (2022/236).

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Informed Consent

Written informed consent was obtained from all participants' parents or legal guardians.

Availability of Data and Materials

Primary data used in this research article will be available on request.

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