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Original Article

Predictors of febrile urinary tract infection caused by extended-spectrum beta-lactamase-producing bacteria

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ABSTRACT

Background. We aimed to evaluate the predictability of extended-spectrum beta-lactamase (ESBL)-producing bacteria (PB) with inflammation markers and hemogram parameters as neutrophil-lymphocyte-ratio (NLR), platelets-lymphocyte-ratio (PLR) and mean-platelet-volume (MPV) in infants with febrile urinary tract infection until the urine cultures are resulted.

Methods. Infants between 2-24 months hospitalized for the first febrile urinary tract infections were grouped as those infected with ESBL-PB and non-ESBL-PB. The demographic and laboratory data (inflammation markers and hemogram parameters) and the ultrasonographical findings were compared between the two groups.

Results. A total of 232 patients were included in the study. The mean age was 8.82 ± 5.68 (2-23) months and 114 (49%) of them were female. *Escherichia coli* was the most common isolated bacteria (79%) followed by *Klebsiella pneumoniae* (15.5%) in urine cultures. There were 88 patients in ESBL-PB infected group and 144 patients in the non-ESBL-PB group. The hematologic parameters such as white blood cell count (WBC) count, NLR, PLR, MPV and procalcitonin (PCT) were similar between the two groups. Only the rate of ultrasonographic abnormalities was significantly higher in infants infected with ESBL-PB (p=0.012). The risk of ESBL-PB positivity in urine cultures increased with age (OR 1.068, 95% CI 1.002-1.139, p=0.045), PCT (OR 1.094, 95% CI 1.011-1.184, p=0.025), and ultrasonographic abnormalities (OR 3.981, 95% CI 1.792-8.845, p=0.001).

Conclusions. Platelet counts, WBC, MPV, NLR, PLR, and PCT were not reliable markers, however having an ultrasonographic abnormality is the most important independent risk factor for prediction of infection with ESBL-PB.

Key words: urinary tract infection, extended-spectrum beta-lactamase-producing bacteria, platelet-to-lymphocyte ratio , neutrophil-to-lymphocyte ratio.

Urinary tract infections (UTI) have been noted as the most common bacterial infections among young children.[1] If UTI is not diagnosed and treated correctly and adequately in children, it can lead to complications such as chronic kidney disease, hypertension, and even end-stage renal failure due to scar formation in kidneys.[1-3] It has been reported that 91% of bacteria causing UTIs in children are Gram-negative bacteria.[4] According to recent reports, *Escherichia coli (E. coli)* and *Klebsiella pneumoniae (K. pneumoniae)* were isolated among the most resistant bacteria in children with UTIs.[5] Especially in the past 10 years, *E. coli* has increased dramatically worldwide as the cause of UTIs.[6] The production of β-lactamase is the main mechanism of resistance against the action of β-lactam antibiotics in Gram-negative bacteria.[7] Besides, extended-spectrum β-lactamase (ESBL) producing Gram-negative bacteria also have resistance to trimethoprim/sulfamethoxazole, fluoroquinolones, and aminoglycosides. This

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makes infection management caused by these pathogens even more complicated.[8,9] The increased resistance to antimicrobial agents results in inappropriate empirical therapy.[9] To avoid this, it is very important to predict the bacteria until urine culture results in UTIs caused by ESBL producing bacteria (ESBL-PB).[10] However, there are a limited number of studies on the presence of a rapid marker in UTIs caused by ESBL-PB.

Recent studies have reported the predictors of upper UTIs, which include systemic inflammatory markers. A significant high C-reactive protein (CRP) has been reported in patients with UTIs caused by *E. coli, Proteus spp., K .pneumoniae, Staphylococcus aureus,* and others, than those without UTI.[11-13] White blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and procalcitonin (PCT) were all reported to be correlated with upper UTI as well as CRP.[14] However, it has not been stated which marker is predictive for ESBL-PB.

The NLR and platelet-to-lymphocyte ratio (PLR) have been proposed as new markers of systemic inflammation.[15] Several studies reported that NLR is a measure of systemic inflammation and it has been used as a guide in the prognosis of bacterial diseases, ischemic heart disease, and several types of cancer.[16] Besides NLR and PLR; the mean platelet volume (MPV) has been evaluated as a biochemical marker in chronic and/or acute inflammatory disorders, including bacterial and rheumatologic diseases.[17,18]

In this study, we aimed to evaluate the predictability of ESBL-PB with inflammation markers including WBC, CRP, PCT, NLR, PLR, and MPV in infants with febrile UTI until the urine culture and antibiogram results are reported. To the best of our knowledge, this is the first study evaluating these associations.

Material and Methods

Patients aged between 2-24 months who were admitted to our pediatrics polyclinic and pediatric emergency unit with fever, diagnosed and hospitalized for the first febrile UTI between 2016 - 2020 were retrospectively analyzed. The diagnosis of febrile UTI was based on the following criteria: 1) body temperature ≥38°C; 2) a positive urine culture collected by catheterization (bacterial growth of ≥100,000 cfu/ml of a single uropathogen). The indications for hospitalization were; age <3 months; having toxic or septic state; having symptoms of urinary obstruction or significant underlying disease and inability to tolerate adequate oral fluids or medications. The families were asked whether the patients had any medical history of urinary system anomalies. Patients with no ultrasonographic imaging in their medical history and those who had ultrasonographic imaging with normal urinary system findings were recorded as patients without a pathological urinary system history. The demographical data of the patients including age, gender, personal medical history about renal pathologies [hydronephrosis (urinary distention of the renal pelvi-calyceal system with/without obstruction to the urinary outflow distal to the renal pelvis), vesicoureteral reflux (VUR), ureteropelvic or ureterovesical obstructions or stenosis, neurogenic bladder, renal hypo-dysplasia, and posterior urethral valve (PUV)], urine dipstick analysis including pyuria (presence of ≥5 white blood cells/hpf in centrifuged urine sample) and nitrite positivity, complete blood count (CBC) including white blood cell (WBC), platelet, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelets volume (MPV), C-reactive protein (CRP), procalcitonin (PCT) and the ultrasonographical findings at the admission to hospital due to UTI were recorded.

Culture plates were incubated in incubators at a mean ambient temperature of 35±2°C, and under normal atmospheric conditions for 18-24 hours; culture plates with bacterial growth of $\geq 10^5$ cfu/ml of a single species on their surfaces were examined. Cultures with mixed growths were excluded. The isolates obtained were identified at a species level using conventional methods,

and fully automated bacterial identification system (Phoenix TM 100, Becton Dickinson, MD, USA). Antimicrobial susceptibilities of isolates were determined using Kirby-Bauer disc diffusion system and fully automated systems in compliance with the recommendations of European Committee on Antimicrobial Susceptibility Testing (EUCAST).[19] The presence of extended-spectrum beta-lactamase (ESBL) was determined using ceftazidime, ceftazidime-clavulanic acid, and cefotaxime-cefotaxime clavulanic acid discs. As a control ATCC 25923 strain of *E. coli* was used.

Patients were grouped as those infected with ESBL-PB and those with non-ESBL-PB. Urine analysis results (pyuria, nitrite positivity), NLR, PLR, MPV, CRP, PCT, and the ultrasonographical findings were compared between the two groups.

The study has been approved by the Ethics Committee of Tepecik Training and Research Hospital (no: 2020/5-8).

Statistical analysis

Analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables between groups. Continuous parameters with normal distribution were compared by the Student's t-test and shown in mean ± standard deviation, whereas those without normal distribution were evaluated by Mann-Whitney U test and defined as median (25th – 75th percentile). Categorical variables between groups were compared using the Chi-square test. We also performed a multivariate statistical analysis of factors related to the ESBL-PB positivity in urine cultures by using a logistic regression model and Odds ratios were evaluated after adjustment for other factors. A p value of <0.05 was considered significant in all statistical evaluations.

Results

A total of 232 patients were included in the study. The demographic data of the patients including age, gender, personal medical history about renal pathologies, pyuria and nitrite positivity, renal ultrasonography findings during febrile UTI are presented in Table I. While 57 cases had a known urinary tract abnormality, there was no defined urinary system pathology in the remaining 175 cases (Table I). The underlying bacterial pathogens are shown in Table I, with *E. coli* being the most common (79%) followed by *K. pneumoniae* with a 15.5% isolation rate. Among patients, 88 (38%) had ESBL-PB and 144 (62%) had non-ESBL-PB yielded in urine cultures (Table I).

When demographic and laboratory findings of patients were compared between the ESBL-PB and non-ESBL-PB groups, none of the demographic findings, urine, or blood parameters were significantly different between the groups (p>0.05). The hematologic parameters such as WBC count, NLR, PLR, MPV, and CRP were similar between the two groups. Only the rate of patients with renal ultrasonographic abnormalities during hospitalization for febrile UTI regardless of their medical history; was significantly higher in infants infected with ESBL-PB (p=0.012, Table II).

Age, PCT levels, and presence of ultrasonographic abnormalities were adopted as confounders in the logistic regression model for the multivariate analysis (Table III). All three variables were found to be independently associated with ESBL-PB positivity in urine cultures of infants with febrile UTI (Table III).

Discussion

Febrile UTI is one of the most common bacterial infections in children and usually causes irreversible renal damage when not diagnosed and treated early. Timely medication and

Table I. Demographical, clinical and microbiological data of patients with febrile urinary tract infection (N=232).

	Results
Age (month), mean ± SD (minimum-maximum)	8.82 ± 5.68 (2-23)
Gender, n (%)	
Female	114 (49.1)
Male	118 (50.9)
History of renal pathology, n (%)	
None	175 (75.4)
Hydronephrosis	19 (8.2)
Vesicoureteral reflux	14 (6.0)
Posterior ureteral valve	7 (3.0)
Renal stone	7 (3.0)
Renal hypoplasia	3 (1.3)
Neurogenic bladder	3 (1.3)
Ureteropelvic obstruction	3 (1.3)
Ureterovesical obstruction	1 (0,4)
Pyuria	211 (90.9)
Nitrite positivity	91 (39.1)
Bacteria	
Escherichia coli, n (%)	184(78.9)
ESBL (+)	69 (37.5)
ESBL (-)	115 (62.5)
Klebsiella pneumoniae, n (%)	36 (15.5)
ESBL (+)	19 (52.7)
ESBL (-)	17 (47.3)
Other ESBL (-) bacteria, n (%)	
Pseudomonas aeruginosa	8 (3.4)
Proteus mirabilis	2 (0.9)
Enterococcus cloacae	1 (0.4)
Citrobacter koseri	1 (0.4)
Ultrasonography findings during UTI, n (%)	
Normal	161 (69.0)
Hydronephrosis	57 (24.6)
Renal stone	8 (3.4)
Renal hypoplasia	4 (1.7)
Renal cysts	2 (0.9)

ESBL: extended-spectrum beta-lactamase, UTI: urinary tract infection

adequate antibiotic duration can considerably improve the disease outcome.[1,2] In the current study, we evaluated characteristics and inflammation markers of 232 children admitted with febrile UTI aged between 2-24 months and their association with ESBL-PB. We found that having ultrasonographic urinary system abnormalities was the most significant independent risk factor for ESBL-PB associated UTI, increasing the risk up to almost 4-fold. This result was in accordance with some recent studies, in which UTIs with ESBL-PB were found to be significantly higher in patients with urinary system anomalies in USG.[10,20,21]

Table II. Comparison of demographic and laboratory data of infants infected with ESBL-PB (extended-spectrum beta-lactamase producing bacteria) and non-ESBL-PB.

Variables	Patients infected with ESBL-PB (n=88)	Patients infected with non-ESBL-PB (n=144)	p
Age (month)	9.88 (4-15)	7 (4-10)	0.056
Gender (female), n (%)	43 (49)	71 (49)	1.000
Urological abnormality in medical history, n (%)	41 (47)	51 (35)	0.160
Pyuria, n (%)	85 (96)	127 (88)	0.102
Nitrite positivity, n (%)	35 (39)	8 (40)	0.996
White blood cell (/mm^3)	13,900 (10,400-19,675)	14,700 (10,375-19,250)	0.463
C-reactive protein (mg/dl)	33.60 (10-89.25)	30.50 (9.83-95.75)	0.893
Procalcitonin (ng/ml)	0.39 (0.18-4.47)	0.16 (0.11-1.03)	0.078
NLR (neutrophil-to-lymphocyte ratio)	1.68 (0.77-2.54)	1.41 (0.76-2.59)	0.603
PLR (platelets-to-lymphocyte ratio)	79.44 (60.38-126.62)	77.75 (53.08-115.6)	0.564
Mean platelet volume (μm^3)	7.8 (7.3-8.4)	7.6 (7.13-8.3)	0.252
Platelets count (× 10^3/ml)	383 (315-458)	380 (297-471)	0.733
Renal ultrasonographic abnormality, n (%)	44 (50)	46 (32)	0.012

Continuous variables are presented as median (25th – 75th percentile).

Table III. Results of multivariate analysis of variables related to extended-spectrum beta-lactamase producing bacteria positivity in urine culture.

Variables	Unit	Odds ratio	95% CI	p
Age	1 month	1.068	1.002-1.139	0.045
Procalcitonin	1 ng/ml	1.094	1.011-1.184	0.025
Ultrasonographic abnormality	Yes	3.981	1.792-8.845	0.001

In many studies, inflammation markers such as WBC, CRP, PCT, NLR, PLR were evaluated in patients with UTIs. These markers were used to differentiate lower UTIs and acute pyelonephritis and to predict renal complications with non-invasive and widely used biomarkers rather than invasive screening methods such as dimercaptosuccinic acid scintigraphy (DMSA) or voiding cystourethrography in most of the studies.[14,22-24] In our study, we evaluated these inflammation markers to predict infections with ESBL-PB, which have been known to have a higher risk for renal complications, to initiate the appropriate treatment, until the urine culture results are out.

Some recent studies have reported that platelets have an important role in the pathogenesis of inflammatory diseases and they can be referred to as an indicator of UTIs.[25] Not only platelet count, but also MPV has been reported as a useful index in the diagnosis of inflammatory diseases, tuberculosis, acute pyelonephritis, and UTIs in some studies.[26-29] MPV has also been reported at high levels in UTIs caused by Gram-positive bacteria.[25,30] Conversely, we have found similar MPV values between the two groups.

The NLR is a substitute marker of inflammation and it has been reported to be useful for the discrimination of systemic bacterial infection and also to predict the outcomes in studies.[31-34] In this study, we aimed to present the NLR as a practical biomarker to predict ESBL-PB in febrile UTI. Han et al.[31] evaluated NLR to predict acute pyelonephritis and they found a significant correlation between elevated NLR and DMSA defect of acute pyelonephritis. Similar results were detected in the study by Lee et al.[35] about the prediction of renal cortical

defect and scar using NLR in children. Gökhan et al.[36] also reported that NLR was significantly higher in patients with a UTI compared to healthy subjects. Contrary to these studies, Kazımoğlu et al.[37] reported that there was no significant difference in NLR between infected and non-infected kidney transplant patients. But they found a significant difference in the NLR ratio between the patients infected with *E. coli* and others.[37] There is no previous study evaluating NLR in patients infected with ESBL-PB and non-ESBL-PB, and in our study, we could not define any difference in NLR levels between the groups.

Platelets to lymphocyte ratio is another inflammation marker and it is used to predict disease activity, prognosis, and survival rates in systemic inflammatory diseases as rheumatologic diseases, cancers, and bacterial and bloodstream infections.[38] The PLR is a new hematological marker related to systemic inflammation result syndrome. It has been reported as a predictor of severe infections, malignity, coronary artery disease, and inflammatory rheumatic diseases in large cohort studies.[39-42] However, PLR has not been reported as predictive as NLR in some studies.[43-45] Similar to those studies, we could not detect differences in PLR between ESBL-PB infected and non-ESBL-PB infected patients.

Many recent studies have reported that inflammation markers could not constantly distinguish renal damage.[24,46,47] Gervaix et al.46 and Smolkin et al.[47] reported that CRP was not sufficient as a predictive marker, with a sensitivity of 83% and 100%, respectively, but a specificity of 18.5%. Shaikh et al.[48] reported a comprehensive review of 24 studies about the usefulness of CRP, ESR, and PCT for renal damage in UTI and they found that none of the tests were accurate enough to allow for detecting renal scarring. They have reported the sensitivity of CRP (cut-off 20 mg/L) and PCT in predicting pyelonephritis is high (94% and 86%, respectively), but specificity varies (39% and 74%, respectively).[48] In contrast, Yi Han et al.[31] reported high CRP levels correlated with renal scarring on a positive DMSA scan. Mushi et al.[3] evaluated CRP levels to predict Gram-negative bacterial UTI and patients with Gram-negative bacterial infections had 3.54 times higher Odds of having positive CRP values. Additionally, many studies have reported high CRP values in patients with UTIs caused by Gram-negative bacteria.[49-51] In our study, we compared CRP values between patients with UTIs caused by ESBL-PB and non-ESBL-PB and we could not find any significant differences between the two groups (p=0.893).

PCT has developed as a favorable marker for diagnosing bacterial infections because of its higher levels in patients infected with bacteria than viruses or non-specific inflammatory diseases. In recent studies, increased levels of PCT have been reported in patients infected with Gram-negative bacteria which are explained by the fact that these pathogens produce exotoxins and cause more inflammation.[52-55] Moreover, Watanabe et al. reported that ESBL-BP positive cases presented higher levels of PCT than cases infected with non-ESBL-PB and they specified that PCT might be a useful marker for detecting patients infected with ESBL-PB and facilitating rapid and appropriate antibiotic treatment.[55] We could not find any difference in PCT levels between the groups. In multivariate analyses, age and PCT emerged as statistically significant risk factors for infection with ESBL-PB, however, we thought that was practically insignificant since the Odds ratios were quite low.

Our study has some limitations. The retrospective nature of the study was one limitation. To rule out false-positive reactions and contamination in the urine culture, only the cases whose urine samples for culture were collected with a urinary catheter were selected. Another limitation was that this group of patients might not represent the whole pediatric population who had a febrile UTI between 2 to 24 months.

In conclusion, this is the first study evaluating the use of easily accessible and cheap parameters including WBC, platelet counts, MPV, NLR,

PLR to predict UTIs caused by ESBL-PB in infants. We could not demonstrate that they were reliable markers for the prediction of ESBL- PB positivity. One possible explanation for these differences can be the small number of UTIs with ESBL-PB in our study. However, we have demonstrated that having renal ultrasonographic abnormality is the most important independent risk factors. Further studies in larger populations would help to decide the predictivity of the inflammation markers and ultrasonographic findings for UTIs caused by ESBL-PB since the number of studies is limited.

Ethical approval

The study has been approved by the Ethics Committee of Tepecik Training and Research Hospital (no: 2020/5-8).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BKD; data collection: ES, MK, GE; analysis and interpretation of results: SAÇ, GE, NY, DA; draft manuscript preparation: ES, FM, BKD. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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