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Building nomogram plots for predicting urinary tract infections in children less than three years of age

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Abstract *Background and purpose:* Urinary tract infections (UTIs) are the most common bacterial infection in young children. This study aimed to formulate nomogram plots for clinicians to predict UTIs in children aged <3 years by evaluating the risk factors for UTIs in these children.
Methods: This retrospective study was conducted at a tertiary medical center from December 2017 to November 2020. Children less than three years of age were eligible for the study if they had undergone both urine culture and urinalysis during the study period. Mixed-effects logistic regression models with a stepwise procedure were used to determine the relationship between outcome (positive/negative UTI) and covariates of interest (e.g., weight percentile, laboratory) for each patient. Nomogram plots were constructed on the basis of significant factors. We repeated the analysis thrice to adapt it to three different medical settings: medical centers, regional hospitals, and local clinics.
Results: In the medical center setting, the two most significant factors were urine leukocyte count $\geq$100 (OR =8.87; 95% CI (Confidence Interval), 4.135—19.027) and urine nitrite level (OR =8.809; 95% CI, 5.009—15.489). The two factors showed similar significance at the regional hospital and local clinic settings. Abnormal renal echo findings were positively correlated with UTI in the medical center setting (OR =2.534; 95% CI 1.757—3.655). Three nomogram plots for the prediction of UTIs were drawn for medical centers, regional hospitals, and local clinics.

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Conclusion: Using the three nomogram plots, frontline doctors can formulate the probabilities of pediatric UTIs for better decision-making.

Introduction

The urinary tract is a common site of infection in both infants and young children.[1] Urinary tract infections (UTIs) are the most common bacterial infections in children aged ≤2 years.[2] The outcomes of UTIs are usually benign; however, an under-diagnosed UTI can lead to multiple comorbidities, including renal scarring[3] and end-stage renal disease.[4] Diagnosing UTIs in older children with better linguistic abilities seems easy. However, younger children tend to have a more atypical presentation of UTIs and higher rates of recurrence than older children.[5,6] Therefore, prompt diagnosis is critical for the initiation of treatment.

The evaluation of UTIs in younger children is challenging because of its nonspecific presentation. The typical signs of UTIs (i.e., increased urinary frequency and dysuria) in adults and older children may not be present or are not easily discernible in younger children. Fever is the most common symptom in infants and may be the sole manifestation in children aged <2 years.[7,8] Therefore, laboratory evaluations of suspected UTIs include urine analysis (UA) and urine culture (UC). The American Academy of Pediatrics recommends that the diagnosis of UTI should include an abnormal UA level plus a positive UC,[9] but the reliability of UA assessments in febrile young children is questionable. Therefore, this study aimed to formulate nomogram plots for clinicians to predict UTIs in children by evaluating most risk factors for UTIs in children less than 3 years of age.

Methods

Study design and subjects

This retrospective study was conducted from December 2017 to November 2020 at MacKay Children's Hospital, a tertiary medical center in northern Taiwan. Children less than three years of age were eligible for the study if they had undergone both UC and UA during the study period. Multiple UTIs in the same patient were counted as separate scenarios. Children were excluded if they had undergone either UC or UA alone, or if they had undergone repeated tests within the same day. We classified paired UA—UC cases as positive for UTI and negative for UTI. UTI was defined when UC was positive (details in the next section). One UA was paired with one UC, which was ordered within 7 days and closest to the time of UA.

Culture technique and definitions

For children under three years of age, all UCs were routinely obtained by urethral catheterization or suprapubic aspiration by experienced doctors, and then sent to the microbiology laboratory in sterile containers using a pneumatic tube. Standard quantitative culture was performed by licensed laboratory technicians. UC was considered positive if it proved the growth of a single bacterium with the following colony counts: 1) any growth by suprapubic aspiration; and 2) more than 5×10^4 CFU/mL by urethral catheterization. None of the urine cultures in our study were collected in urine bags.[10]

Statistical analysis

The data analyses included descriptive and inferential statistics. Descriptive statistics, including estimated mean and standard deviation for continuous variables (e.g., age, erythrocyte, etc.), as well as percentages and frequencies for categorical variables (e.g., sex, UA, etc.), were tabulated (Table 1). Although many of the VUR grades were made after the UTI episodes, it is a preexisting condition only undetected before these patients came to our hospital. Therefore, we decided to put the factor in the analysis, hoping to help the diagnosis of future UTIs for patients with confirmed VUR. For inferential statistics, Student's t-test or Fisher's exact test was used. To determine the relationship between outcome (positive/negative UTI) and covariates of interest (e.g., weight percentile, laboratory, etc.), mixed-effects logistic regression models with a stepwise procedure were used for each patient (Table 2). The receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to assess the performance of the binary classification models. In addition, we used Youden's index[11] to calculate an optimal cutoff point based on the selected model. Nomogram plots were constructed based on these factors. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant. All analyses were performed using the R 3.6.3 software (www.r-project.org) for Windows.

We repeated the analysis thrice to adapt it to three different medical settings: medical centers, regional hospitals, and local clinics (Table 2). We excluded blood test-related factors and renal echography in the model for local clinics, analyzing only patients' characteristics and urinalysis. In the model for regional hospitals, blood test results were added. Finally, we used renal echography findings in the model for medical centers.

Results

Demographic and clinical characteristics

A total of 1271 patients were enrolled for both urinalysis and urine culture. Data were collected for 1529 UA—UC pairs and sent for further analysis; 171 patients had more than one UA—UC pair. Of the 1529 cases analyzed, 688 were

Table 1 Factors that were analyzed.

Age[a]
Sex[b]
Weight percentile[c]
Whether patient was febrile[d]
Urinalysis: leukocyte esterase,[e] nitrite, bacteria, erythrocyte, leukocyte[f]
Blood test: WBC count, band form,[g] neutrophils, platelet, lymphocyte, C-reactive protein
Positive renal echography findings[h]
Whether VCUG[i] showed any findings

White blood cells (WBCs); voiding cystourethrography (VCUG).
[a] The age unit was months.
[b] Male patients were coded as 1; female patients were coded as 0.
[c] The weight percentile was interpreted using the WHO Child Growth Standards. These standards were collected in a WHO multicenter growth reference study.
[d] Fever was defined as rectal temperature or tympanic membrane temperature (measured by an infrared thermometer) ≥38.0 °C (100.4 °F). Fever was categorized as fever or non-fever.
[e] Leukocyte esterase was categorized into leukocyte esterase 0: 0, trace, or 1+; and leukocyte esterase 1: 2+ or 3+.
[f] Leukocytes were categorized as leukocyte 0: <5; leukocyte 1: 5≤ value <100; and leukocyte 2: ≥100.
[g] Band form was categorized into 0 and >0.
[h] Renal echography findings were considered positive if the following were written in the report: 1) unilateral or bilateral hydronephrosis and/or pelvic dilatation; 2) duplex collecting system; 3) swelling and relatively large kidney; 4) multicystic dysplastic kidney (MCDK); and 5) hydroureter/dilated upper ureter/cyclic dilatation of the renal pelvis.
[i] VCUG: voiding cystourethrography

Table 2 Covariates of interest in each clinical setting: medical centers, regional hospitals, and local clinics.

	Medical center	Regional hospital	Local clinic
1.	Age	Age	Age
2.	Sex	Sex	Sex
3.	Weight percentile	Weight percentile	Weight percentile
4.	Leukocyte esterase	Leukocyte esterase	Leukocyte esterase
5.	Nitrite	Nitrite	Nitrite
6.	Bacteria	Bacteria	Bacteria
7.	Erythrocytes	Erythrocytes	Erythrocytes
8.	Leukocytes	Leukocytes	Leukocytes
9.	WBCs	WBCs	VUR grade
10.	Band form	Band form	Fever
11.	Neutrophils	Neutrophils	
12.	Platelets	Platelets	
13.	Lymphocyte	Lymphocytes	
14.	CRP	CRP	
15.	VUR grade	VUR grade	
16.	Fever	Fever	
17.	Final finding on renal echo		

White blood cells (WBCs); C-reactive protein (CRP); Vesicoureteral reflux (VUR).

diagnosed as showing UTI and 841 as non-UTI cases. The mean age was 10.90 months, and 415 patients (60.2%) were men. Except for fever status and lymphocyte count in the blood tests, the differences among all other parameters were statistically significant between the two groups. In the group diagnosed with UTI, we noted younger age, more male patients, heavier weight, and more abnormal urinalysis results (leukocyte esterase, nitrite, bacteria, erythrocytes, and leukocytes) and blood test results (white blood cell count, band form, neutrophil, platelet, and C-reactive protein). Moreover, UTI patients had a higher percentage of positive renal echography reports and vesicoureteral reflux (VUR) findings (Table 3). Renal echography findings were considered positive if the following were written in the renal echography report: 1) unilateral or bilateral hydronephrosis and/or pelvic dilatation; 2) duplex collecting system; 3) swelling and relatively large kidney; 4) multicystic dysplastic kidney (MCDK); and 5) hydroureter/dilated upper ureter/cystic dilatation of the renal pelvis.

Three nomogram plots for three clinical settings: medical centers, regional hospitals, and local clinics

Factors predicting UTIs were selected using mixed-effects logistic regression models with a stepwise procedure. Nomogram plots were drawn for three different clinical settings: medical centers, regional hospitals, and local clinics. A total of 1031 paired UA—UC data were analyzed for the medical centers and regional hospital settings (499 UTI cases and 532 non-UTI cases), because the rest 498 pairs did not have completed blood results (e.g., missing CRP levels). All 1529 paired data were analyzed for the local clinic setting (688 UTI cases and 841 non-UTI cases).

The selected significant factors are listed for medical centers (Table 4), regional hospitals (Table 5), and local clinics (Table 6). On the basis of stepwise selection, nine factors (age, weight percentile, urine leukocyte counts, urine nitrite, urine leukocyte esterase, urine bacteria, blood white blood cell (WBC) counts, serum C-reactive protein (CRP) levels, and renal echography results) were included in the model for medical centers. For regional hospitals, the eight chosen factors were the same as those

Table 3 Demographic and clinical characteristics.

	No UTI (n = 841) Mean (sd) or (%)	UTI (n = 688) Mean (sd) or (%)	P value
Age	14.32 (12.54)	10.90 (10.23)	<0.001
Male	306 (36.4%)	415 (60.2%)	<0.001
Weight percentile	0.40 (0.31)	0.49 (0.29)	<0.001
UA			
Leukocyte esterase 1	365 (43.4%)	578 (84.0%)	<0.001
Nitrite	31 (3.7%)	288 (41.8%)	<0.001
Bacteria	189 (22.5%)	486 (70.7%)	<0.001
Erythrocytes	6.74 (17.46)	13.24 (21.83)	<0.001
Leukocytes (%)			<0.001
0	264 (31.4%)	41 (6.0%)	
1	513 (61.0%)	253 (36.7%)	
2	64 (7.6%)	395 (57.3%)	
Blood test			
WBCs	11.89 (6.45)	15.79 (6.45)	<0.001
Band form	159 (28.4%)	84 (16.6%)	<0.001
Neutrophils	46.92 (19.69)	50.69 (15.94)	0.001
Platelets	317.77 (129.23)	373.51 (125.70)	<0.001
Lymphocytes	37.24 (18.32)	35.53 (15.47)	0.102
CRP (mg/dL)	2.95 (4.73)	4.90 (5.31)	<0.001
VUR grade (%)			<0.001
0	820 (97.5%)	609 (88.4%)	
1	1 (0.1%)	11 (1.6%)	
2	5 (0.6%)	17 (2.5%)	
3	5 (0.6%)	19 (2.8%)	
4	4 (0.5%)	16 (2.3%)	
5	6 (0.7%)	17 (2.5%)	
Fever	592 (70.4%)	516 (74.9%)	0.057
Renal echo finding	155 (18.4%)	370 (53.8%)	<0.001

White blood cells (WBCs); C-reactive protein (CRP); Vesicoureteral reflux (VUR).

for medical centers, except for renal echography. Finally, five factors (age, sex, urine leukocyte count, urine nitrite, and urine leukocyte esterase) were chosen for the local clinic model. A comparison of these factors is shown in Table 7.

In the medical center setting, the two most significant factors were urine leukocyte ≥100 (OR =8.87; 95% CI (Confidence Interval), 4.135–19.027) and urine nitrite (OR =8.809; 95% CI 5.009–15.489). The two factors showed similar significance in the regional hospital and local clinic settings. Abnormal renal echo findings were positively correlated with UTIs in the medical center setting (OR =2.534; 95% CI 1.757–3.655). Male sex was positively correlated with UTI in the local clinic settings (OR =3.163; 95% CI 2.256–4.436), while this factor was not used in the other two settings. Other results are listed in Tables 4–6

Three nomogram plots for the prediction of UTIs were drawn for medical centers (Fig. 1), regional hospitals (Fig. 2), and local clinics (Fig. 3). The likelihood calculated by ROC analysis to predict UTIs for medical centers, regional hospitals, and local clinics was 90.33%, 89.33%, and 91.13%, respectively (Fig. 4). All three models had high and significant accuracies in predicting UTIs. We used the Youden index to identify cutoff points in each ROC, yielding

Table 4 Significant factors for the medical center setting.

Variables	Coefficient (S.E.)	P value	OR (95% CI)
WBCs	0.038 (0.014)	0.0068	1.039 (1.011, 1.068)
Leukocyte 1	0.647 (0.300)	0.0310	1.910 (1.061, 3.438)
Leukocyte 2	2.183 (0.389)	<0.001	8.870 (4.135, 19.027)
Nitrite	2.176 (0.288)	<0.001	8.809 (5.009, 15.489)
Age	−0.055 (0.011)	<0.001	0.946 (0.927, 0.966)
Renal echo finding	0.930 (0.187)	<0.001	2.534 (1.757, 3.655)
CRP	0.038 (0.020)	0.0493	1.039 (1.000, 1.080)
Leukocyte esterase 1	0.632 (0.247)	0.0105	1.881 (1.159, 3.051)
Bacteria	0.443 (0.204)	0.0298	1.558 (1.044, 2.323)
Weight percentile	0.840 (0.300)	0.0050	2.317 (1.288, 4.170)

White blood cells (WBC); C-reactive protein (CRP); standard error (S.E.); odds ratio (OR); confidence interval (CI).

Table 5 Significant factors for the regional hospital setting.

Variable	Coefficient (S.E.)	P value	OR (95% CI)
WBCs	0.047 (0.013)	<0.001	1.048 (1.021, 1.076)
Leukocyte 1	0.762 (0.296)	0.0099	2.143 (1.201, 3.824)
Leukocyte 2	2.433 (0.382)	<0.001	11.388 (5.385, 24.083)
Nitrite	2.187 (0.283)	<0.001	8.908 (5.118, 15.503)
Age	−0.058 (0.010)	<0.001	0.943 (0.924, 0.963)
CRP	0.053 (0.019)	0.0058	1.055 (1.016, 1.095)
Leukocyte esterase 1	0.715 (0.241)	0.0030	2.044 (1.274, 3.279)
Bacteria	0.435 (0.199)	0.0290	1.545 (1.046, 2.282)
Weight percentile	0.862 (0.295)	0.0035	2.368 (1.328, 4.223)

White blood cells (WBC); C-reactive protein (CRP); Standard error (S.E.); odds ratio (OR); confidence interval (CI).

Table 6 Significant factors for the local clinic setting.

Variable	Coefficient (S.E.)	P value	OR (95% CI)
Leukocyte 1	1.079 (0.258)	<0.001	2.943 (1.776, 4.877)
Leukocyte 2	2.941 (0.348)	<0.001	18.929 (9.561, 37.478)
Nitrite	2.556 (0.270)	<0.001	12.883 (7.593, 21.860)
Male	1.152 (0.173)	<0.001	3.163 (2.256, 4.436)
Age	−0.034 (0.007)	<0.001	0.967 (0.953, 0.981)
Leukocyte esterase 1	0.987 (0.209)	<0.001	2.684 (1.782, 4.043)

White blood cells (WBC); C-reactive protein (CRP); standard error (S.E.); odds ratio (OR); confidence interval (CI).

accuracies of 0.84, 0.83, and 0.85, for the medical center, regional hospital, and local clinic models, respectively. The cutoff points, sensitivities, 1 - specificities, accuracies, and AUCs are listed in Table 8. For some local clinics, urine dipstick without urine leukocyte count could be the only option for urine examination, so we created another nomogram without urine leukocyte count (in supplementary data). With only four factors excluding the urine leukocyte count, the likelihood to predict UTIs was 90.42%, which still had high and significant accuracies in predicting UTIs, but the compactness of the nomogram will be sacrificed.

Discussion

Many of urinalysis-driven protocols of UTI use arbitrary cutoff values of urinalysis components to guide management. However, the main purpose of our nomogram is to provide probabilities, but not cutoffs, for UTIs in children. Urinalysis is widely used by clinicians to predict UTI in young children. Except for pyuria,[12–14] other indicators, such as the levels of leukocyte esterase, nitrites, and bacteria, can also help in the diagnosis of UTIs.[15,16] However, no individual component of urinalysis is both highly sensitive and specific. For example, pyuria in children can also be found in other febrile illnesses, including appendicitis, Kawasaki disease, and roseola infantum.[17]

Nomograms are graphical representations of equations that predict medical outcomes. By using a points-based system, a patient accumulates points based on levels of the variables. The effect of the variables on the specific outcome is represented in the format of axes (Figs. 1–3), and risk points are attributed according to the predictive importance of the variable of interest. To make it more manageable, the formula will easily be transformed into a user-friendly nomogram-based online tool for prediction of UTIs in children. By simply keying in the parameters needed, the online calculators can provide physicians the probabilities for UTI within seconds. We hope the future online tool could also contribute to a better patient-doctor communication for all pediatricians.

The significant factors listed in Table 7 were previously reported to be related to UTIs.[18,19] For example, UTIs are more often found in younger children, especially toddlers. In a meta-analysis, Shaikh et al. showed that the pooled prevalence rates of febrile UTIs in female patients aged 0–3 months, 3–6 months, 6–12 months, and >12 months were 7.5%, 5.7%, 8.3%, and 2.1%, respectively.[20,21] Obesity is also associated with febrile UTIs, and obese children have a higher risk of developing UTIs than nonobese children.[22] Childhood obesity is a complex disorder that is often accompanied by increased inflammation, altered adipokine signaling, metabolic changes, and epigenetic regulation that have clinically significant impacts on immune response.[22] Another explanation is that it is more difficult for parents to implement proper perineal hygiene on obese infants. All these factors might be possible reasons for the association of weight percentile and UTI in children. In our study, the weight percentile factor was chosen in the nomogram plots for medical centers and regional hospitals. The variable remained statistically significant for the local clinics model, but since the addition of it did not increase the fitness, we dropped it from the nomogram to reduce the extra parameters needed.

Previous studies have focused on the sensitivity and specificity of each urinalysis parameter.[13,23] However, pyuria may not appear in approximately 10%–20% of UTI cases in children.[24] Williams et al., in a meta-analysis, found that the sensitivity and specificity of the abnormal urine leukocyte count were 0.74 and 0.86, respectively, which

Table 7 Comparison of significant factors in three clinical settings.

AUC	Medical center 0.9033	Regional hospital 0.8933	Local clinic 0.9133
Variables	Age	Age	Age
	Weight percentile	Weight percentile	Sex
	Urine leukocyte counts	Urine leukocyte counts	Urine leukocyte
			Urine nitrite
	Urine nitrite	Urine nitrite	Urine leukocyte esterase
	Urine leukocyte esterase	Urine leukocyte esterase	
	Urine bacteria	Urine bacteria	
	Blood WBC counts	Blood WBC counts	
	Serum CRP levels	Serum CRP levels	
	Renal echo results		

Area under the curve (AUC); white blood cell (WBC); C-reactive protein (CRP).

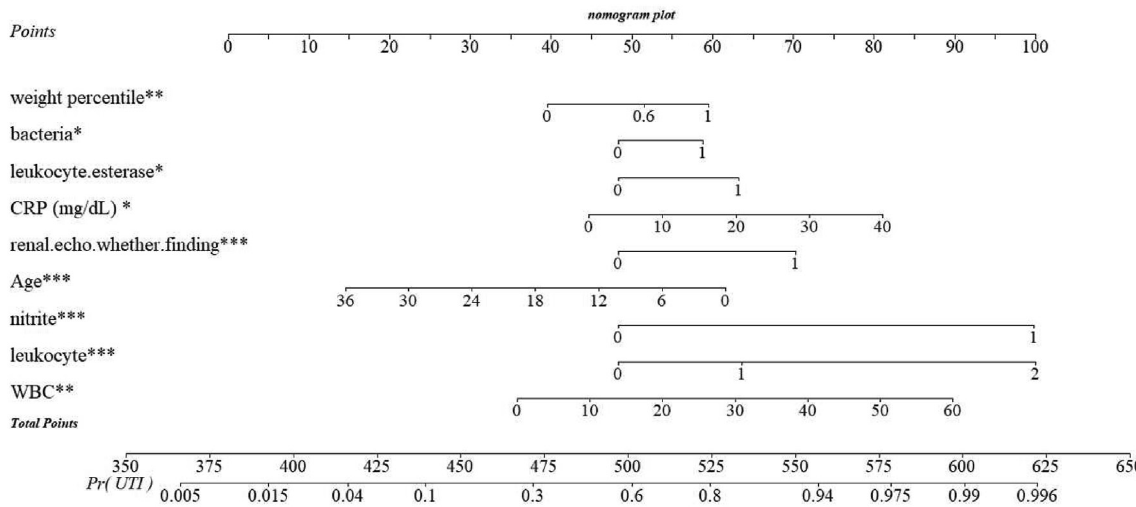

Figure 1. Nomogram of the prediction model for pediatric urinary tract infections for the medical center setting.

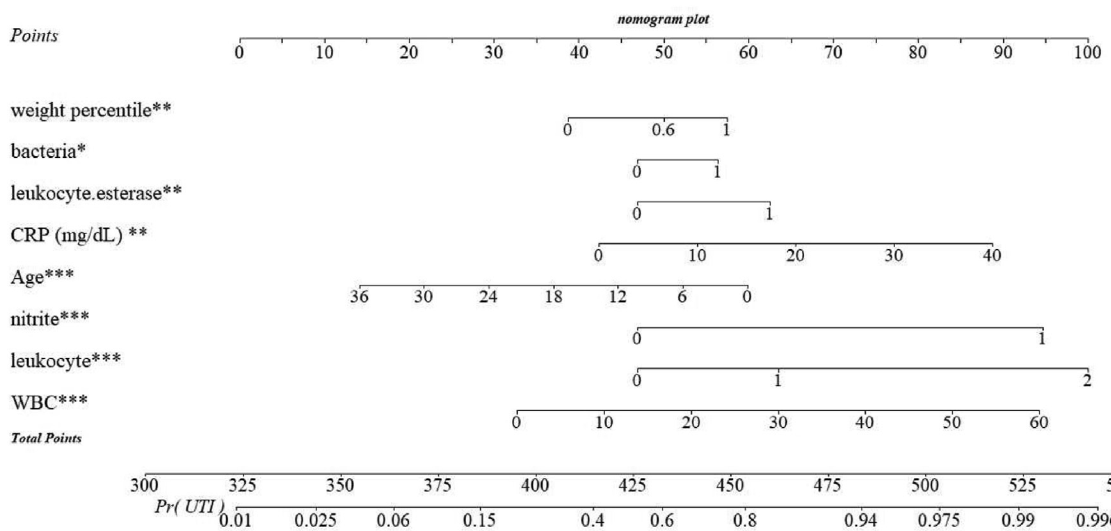

Figure 2. Nomogram of the prediction model for pediatric urinary tract infections for regional hospital setting.

were similar to those of positive urine leukocyte esterase (sensitivity, 0.79; specificity, 0.87).[13] Urine nitrite is well known to show high specificity, but low sensitivity. Leukocyte esterase and nitrite are believed to be better predictors of UTI in older children but less reliable in infants, since infants have more frequent micturition, which does not allow for the development of sufficient concentrations of these substrates.[25] Detection of bacteriuria by microscopy with Gram staining is the single best test and, if available locally and reported rapidly, is the only test that would need to be performed to guide empirical treatment of children with antibiotics.[13] Similarly, the absence of bacteriuria does not exclude a diagnosis of UTI.[26]

Previous studies have stated that blood tests such as white blood cell counts, erythrocyte sedimentation rates, and C-reactive protein levels are not distinguishable between infants with and without UTIs.[27,28] However, in our study, when analyzed together with other variables, the white blood cell count and C-reactive protein level could make predictions more accurate in both the medical center and regional hospital models. Moreover, the addition of positive renal echo findings as a factor could marginally increase the accuracy of prediction from 0.83 for the regional hospital model to 0.84 for the medical center model. Although some researchers questioned the yield of the routine renal sonogram in the management of young children with a first simple UTI,[29] others considered that renal sonograms are necessary to exclude severe congenital renal scarring, obstructive uropathy, and renal abscess at the first incidence of febrile UTI and help determine the need for subsequent clinical imaging studies.[30]

The top four pathogens in our study were *E. coli*, *P. mirabilis*, *K. pneumoniae*, and *E. faecalis* during the study

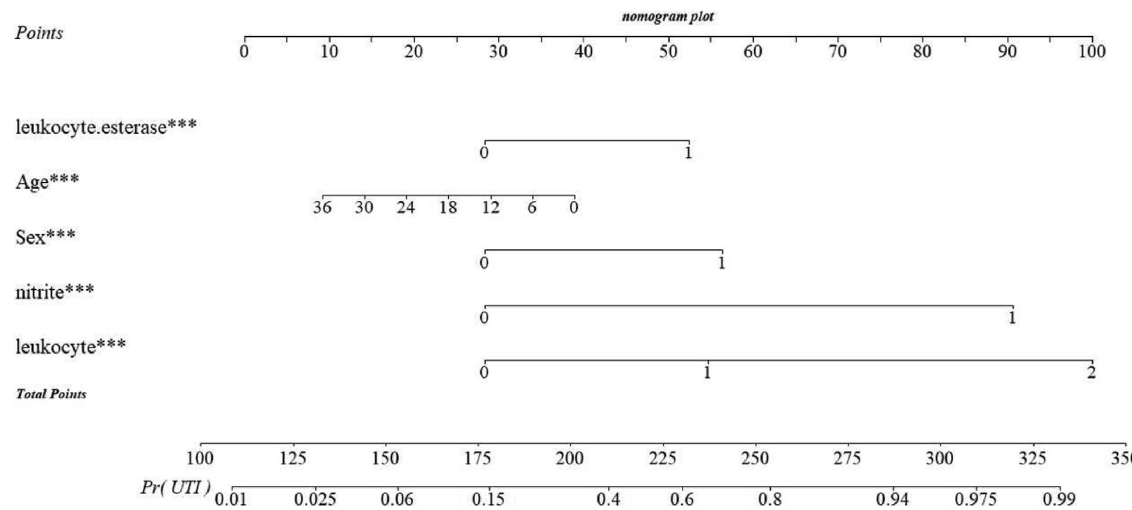

Figure 3. Nomogram of the prediction model for pediatric urinary tract infections for the local clinic setting.

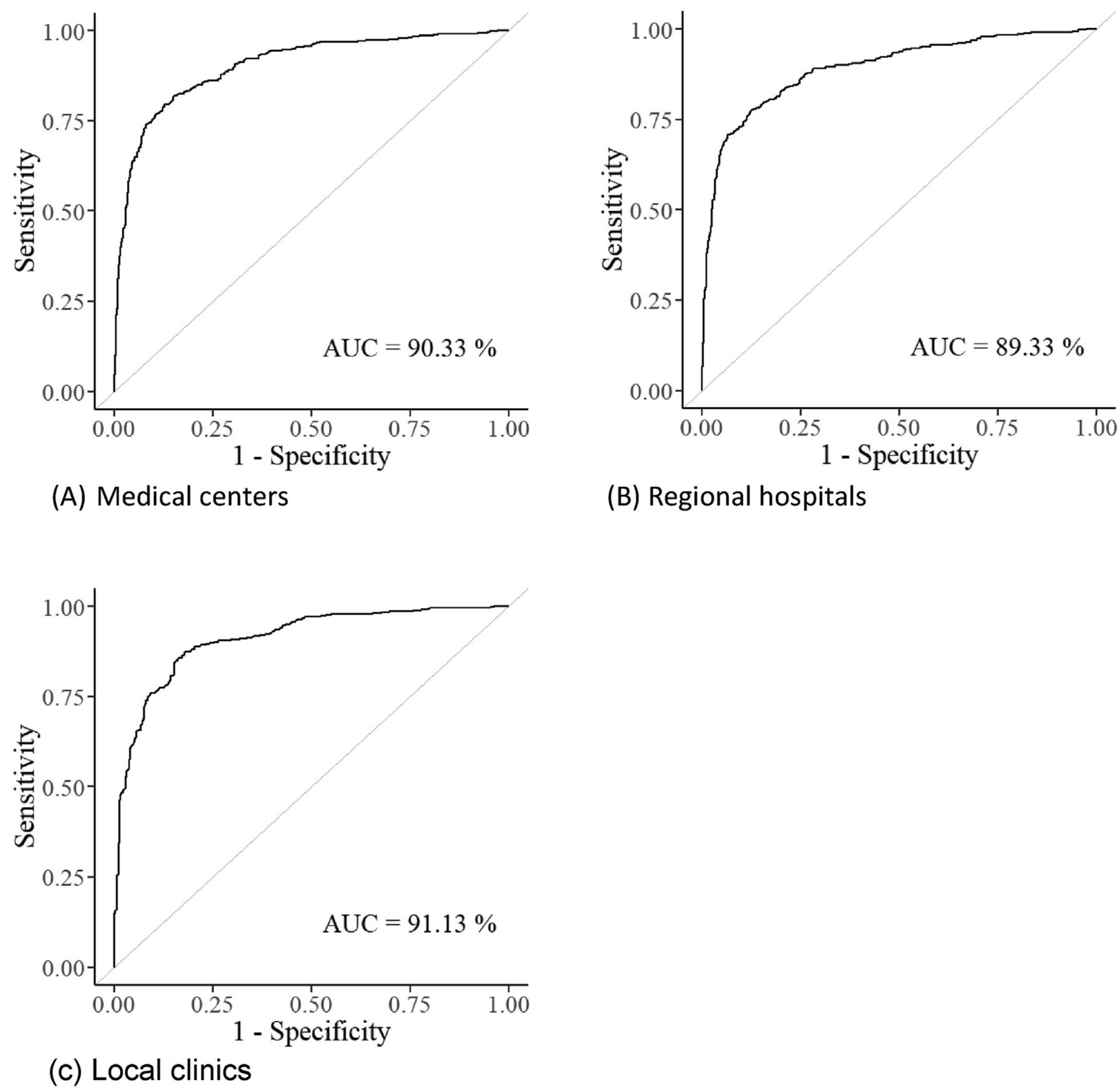

Figure 4. ROC curves for (A) medical centers; (B) regional hospitals; and (C) local clinics. The likelihood calculated by ROC analysis to predict UTIs for medical centers, regional hospitals, and local clinics was 90.33%, 89.33%, and 91.13%, respectively.

Table 8 Comparison of results from the ROC analysis.

	Medical center	Regional hospital	Local clinic
Cutoff point	0.50	0.49	0.31
Sensitivity	0.80	0.78	0.87
1-Specificity	0.13	0.13	0.18
Accuracy	0.84	0.83	0.85
AUC	90.33%	89.33%	91.13%

Receiver operating characteristic (ROC); area under the curve (AUC).

period. In the 688 cases, *E. coli* was the most common causative organism in 70% of the cases. In previous studies, male infants with VUR were more likely to present with UTIs caused by pathogens other than *E. coli*.[18,31–33] Interestingly, *K. pneumoniae* was found in 11 UTI patients with VUR in our study. The underlying mechanism is still unknown and requires further study.

Our study had several limitations. First, we did not record the circumcision histories of the male participants. Uncircumcised male infants with fever have a four-to eight-fold higher prevalence of UTI than circumcised male infants.[34,35] However, most of our male infants were not circumcised, since circumcision is not commonly performed in newborns in Taiwan. Second, the male sex factor was left unadjusted in the local clinic model, although the factor was only significant in pediatric UTIs during the first year of age. However, to simplify our nomogram plot, we decided to use it in our model. Finally, because the number of patients analyzed in the local clinic setting was more than those for the medical center and regional hospital settings, we were unable to compare the accuracies of the two models in our study. In terms of accuracy, the local clinic model appeared to perform better than the medical center model (0.85 vs. 0.84), but this is not the case considering the population size analyzed.

Conclusion

We successfully constructed three nomogram plots for predicting UTIs in children less than three years old. The three nomogram plots were designed for medical centers, regional hospitals, and local clinics. By simply filling in the parameters, frontline doctors can formulate the probability of UTIs for better decision-making and communication with the patients' parents.

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Conflict of Interest

The authors declare no potential conflicts of interest to disclose.

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Appendix A Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.08.006.