Predictive Value of Systemic Immune-Inflammation Index Combined with Distal Ureteral Diameter Ratio for Early Breakthrough Urinary Tract Infection in Children with Primary Vesicoureteral Reflux

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AIM: To investigate predictive value of the systemic immune-inflammation index (SII) combined with the distal ureteral diameter ratio (UDR) for early breakthrough urinary tract infection (BT-UTI) in children with primary vesicoureteral reflux (VUR).
METHODS: A retrospective analysis was conducted on 150 VUR patients admitted to ShangHai Children's Hospital from January 2021 to December 2023. Patients were divided into the early BT-UTI group ($n = 52$) and the non-earlyBT-UTI group ($n = 98$) based on whether early BT-UTI occurred. Univariate and binary logistics regression analyses were performed to identify factors influencing early BT-UTI in VUR children. Pearson correlation analysis was used to assess the relationship between variables, and receiver operating characteristic (ROC) curve was employed to evaluate the predictive value of SII combined with UDR for early BT-UTI in VUR children.
RESULTS: Comparisons of age, gender, body mass index (BMI), neutrophils (NEU), lymphocytes (LYM), red blood cells (RBC), white blood cells (WBC), comorbidities, length of hospital stay, and caregiver education level showed no statistically significant differences ($p > 0.05$). Differences in reflux grade, UDR, SII, and platelets (PLT) between the groups were statistically significant ($p < 0.05$). According to Pearson linear correlation analysis, SII was negatively correlated with LYM, and positively correlated with PLT and NEU ($r = 0.366$ and 0.839, respectively; $p < 0.05$). UDR was unrelated to NEU and LYM, and positively correlated with PLT ($r = 0.280$, $p < 0.05$), and SII was positively correlated with UDR ($r = 0.162$, $p < 0.05$). Binary logistic regression analysis indicated that UDR and SII were factors influencing early BT-UTI in VUR children (OR = 1.171 and 5.306, respectively; 95% confidence interval (CI) = 1.099–1.249 and 2.841–9.912, respectively; $p < 0.05$). The combined variables had an area under the curve (AUC) of 0.832 with a standard error of 0.032 (95% CI: 0.768–0.895), Youden index = 0.53, sensitivity of 90.4%, and specificity of 62.2%. The combined index had an AUC closest to 1, indicating the highest predictive value.
CONCLUSIONS: UDR combined with SII boasts a high predictive value for early BT-UTI in VUR children.

Keywords: systemic immune-inflammation index; distal ureteral diameter ratio; children; primary vesicoureteral reflux; urinary tract infection

Introduction

Primary vesicoureteral reflux (VUR) in children refers to the retrograde flow of urine from the bladder into the ureter and renal pelvis due to abnormalities at bladder-ureter junction [1]. The incidence of this condition is low in healthy children but increases to 20%–50% in children with urinary tract infections (UTIs) [2]. VUR and recurrent UTIs can lead to persistent kidney damage and scarring, potentially causing hypertension and chronic kidney damage, posing a serious threat to children's health. Recent years have seen advancements in medical research where more attention is turned to exploring early diagnosis and effective treatment strategies for primary VUR in children. Thus, being able to predict and prevent early breakthrough urinary tract infections (BT-UTIs), a common complication of VUR, is particularly crucial [3]. At present, diagnosis of VUR is generally confirmed through imaging findings like those from voiding cystourethrography, based on which treatment plans are conceptualized or formulated. However, these diagnostic methods are often invasive and have limited predictive value for BT-UTIs [4]. The systemic immune-inflammation index (SII) and distal ureteral diameter ratio (UDR), as emerging biomarkers and anatomical parameters, have shown significant potential in predicting and diagnosing various diseases in recent years. Newly recognized as an inflammatory marker, SII shows excellent and stable performance in reflecting the human body's local immune response and systemic inflammatory response [5]. UDR, on the other hand, reflects the anatomical features of the distal ureter and may be related to the occurrence of VUR and the susceptibility to UTIs [6].

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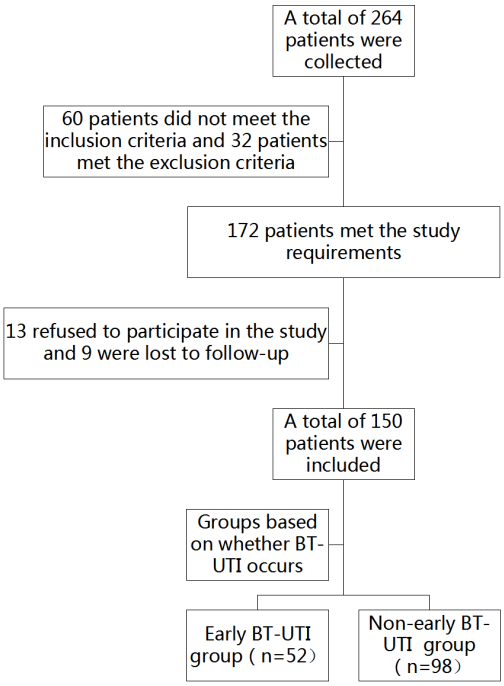

Fig. 1. Flowchart of patient recruitment, selection and categorization. Abbreviation: BT-UTI, breakthrough urinary tract infection.

This study aims to evaluate the combined utility of SII and UDR in predicting early BT-UTIs in children with VUR. The goal is to alleviate their suffering, guide evidence-based clinical decision making, and improve treatment outcomes and quality of life.

Materials and Methods

Research Subjects

A total of fourteen variables were investigated in this study. The study's sample size is supposed to be 5 to 20 times that of the number of variables, taking into account 20% of the subjects recruited would not be included eventually. The proposed sample size of this study is between 84 and 336. A random number table method was used to reduce regional bias and influence of confounding factors. Out of the 264 subjects who were recruited and screened, 150 patients were finally included (Fig. 1). A retrospective analysis was conducted on 150 VUR patients admitted to our hospital between January 2021 and December 2023. The inclusion criteria of this study are as follows: (1) patients who met the clinical diagnosis criteria for VUR [7]; (2) patients aged between 1 and 120 months; (3) patients with complete clinical data available; and (4) patients who underwent continuous prophylactic antibiotic therapy according to the guidelines of the American Urological Association (AUA) [8]. The exclusion criteria are as follows: (1) patients with secondary vesicoureteral reflux; (2) patients who were lost to follow-up during the study period; (3) patients with ureteral ectopia or cysts; and (4) patients with infections in other areas, for example, inflammation of abdominal organs. This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Medical Ethics Committee of the Shanghai Children's Hospital, of Medicine Shanghai Jiao Tong (2024R165-E01). Informed consent was obtained from the patients or their families after having been fed with the information about the study.

Research Methods

Patients were divided into the early BT-UTI group ($n = 52$) and the non-early BT-UTI group ($n = 98$) based on whether early BT-UTI occurred. Diagnosis of early BT-UTI was made for patients with a white blood cell count exceeding 5 per high-power field in routine urine test, accompanied by a fever above 38.5 °C, during continuous prophylactic antibiotic therapy after a VUR diagnosis [9,10]. UDR was calculated by measuring the maximum diameter of the intrapelvic ureter and dividing it by the distance between the first and third lumbar vertebrae [11]. These anatomical measurements were performed by professional urologists and imaging experts in our hospital, who have rich professional knowledge and clinical experience, and are able to accurately interpret imaging data, in order to ensure accuracy and reliability of measurement results, and consolidate diagnosis outcomes and facilitate disease treatment. Venous blood samples were collected from all subjects on the

first morning at admission to measure neutrophils (NEU), platelets (PLT), and lymphocytes (LYM) for SII calculation using formula in the following [12]: SII = NEU × PLT/LYM.

Missing data in this study were handled by deleting samples containing missing values. For potential confounding factors, correlation analysis or multiple regression analysis was conducted in this study to identify and quantify their impact on the study results and to ensure the accuracy and reliability of the conclusions.

Statistical Analysis

The collected experimental data were analyzed using SPSS27.0 (International Business Machines Corporation, Armonk, NY, USA), and the data were subjected to Bartlett's test to assess homogeneity of variances. Shapiro–Wilk test was used for assessing data normality. Normally distributed continuous data are presented as mean ± standard deviation. The independent sample *t*-test was used for data comparison. Categorical data are expressed as cases or rates. Chi-squared test or Fisher's exact test was used for comparison of categorical data. Influencing factors identified as significant in the univariate analysis were included in the binary logistic regression analysis of early BT-UTI occurrence in children with VUR. The area under the curve (AUC), 95% confidence interval (CI), and sensitivity and specificity of the receiver operating characteristic (ROC) curve were used to evaluate the predictive value of SII combined with UDR for early BT-UTI occurrence in children with VUR, and Pearson correlation was used to analyze the association between variables, with $p < 0.05$ denoting statistically significant difference.

Results

Univariate Analysis of Factors Influencing Early BT-UTI in Children with VUR

Comparisons of age, gender, body mass index (BMI), NEU, LYM, red blood cell count, white blood cell count, comorbidities, length of hospital stay, and caregiver's level of education showed no statistically significant differences ($p > 0.05$). However, comparisons of reflux grade, UDR, SII, and PLT revealed statistically significant differences ($p < 0.05$), as shown in Table 1.

Correlation Analysis of Variables

According to the Pearson linear correlation analysis, SII was negatively correlated with LYM, and positively correlated with PLT and NEU ($r = 0.366$ and 0.839, respectively; $p < 0.05$). UDR was not associated with NEU and LYM, but was positively correlated with PLT ($r = 0.280$, $p < 0.05$). SII was positively correlated with UDR ($r = 0.162$, $p < 0.05$), as shown in Table 2.

Binary Logistic Regression Analysis of Influencing Factors

Reflux grade (1~2 = 0, 3 = 1, 4 = 2, 5 = 3), UDR, and SII were employed as independent variables and early BT-UTI status as dependent variables (early BT-UTI = 1, no early BT-UTI = 0) in the binary logistic regression analysis, with PLT excluded as a confounding factor. For continuous variables like UDR and SII, original values were used in the analysis. The results of the binary logistic regression analysis indicated that UDR and SII were influencing factors for early BT-UTI in children with VUR (OR = 1.171 and 5.306, respectively; 95% CI = 1.099–1.249 and 2.841–9.912, respectively; $p < 0.05$), as shown in Table 3.

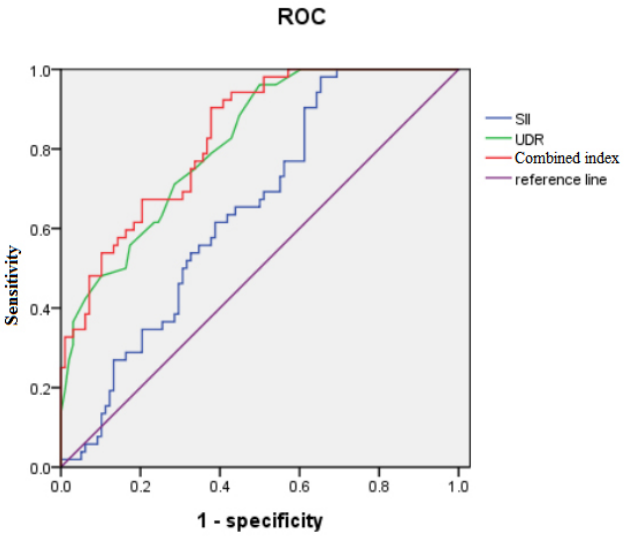

Fig. 2. ROC curve. The estimated area under the ROC curve for the combined SII-UDR index is closest to 1, indicating the highest predictive value for early BT-UTI in children with VUR.

ROC Curve Analysis

The ROC analysis results indicated that the estimated area under the curve (AUC) for UDR was 0.814 with a standard error of 0.034 (95% CI: 0.747–0.881) and Youden index of 0.46, resulting in a sensitivity of 96.2% and specificity of 50.0%. For SII, the estimated AUC was 0.648 with a standard error of 0.044 (95% CI: 0.561–0.735) and Youden index of 0.33, resulting in a sensitivity of 98.1% and specificity of 34.7%. In the case of the combined UDR-SII index, the estimated AUC was 0.832 with a standard error of 0.032 (95% CI: 0.768–0.895) and a Youden index of 0.53, resulting in a sensitivity of 90.4% and specificity of 62.2%. The combined index has the highest predictive value for early BT-UTI in children with VUR, given that its estimated AUC is closest to 1 (Table 4 and Fig. 2).

Discussion

VUR can not only cause UTIs but also lead to kidney damage, hypertension, and renal failure. early BT-UTI refers to

Table 1. Univariate analysis of factors influencing early BT-UTI in children with VUR.

Baseline data		Early BT-UTI group (n = 52)	Non- early BT-UTI group (n = 98)	t/χ^2 value	p-value
Age (months)	<40	15	33	0.373	0.830
	40∼80	19	34		
	≥80	18	31		
Gender	Male	27	50	0.011	0.916
	Female	25	48		
Reflux grade	1∼2	2	6	8.997	0.029
	3	6	32		
	4	29	40		
	5	15	20		
BMI (kg/m^2)		19.89 ± 1.18	20.04 ± 1.11	0.791	0.430
UDR		0.52 ± 0.06	0.43 ± 0.08	7.315	<0.001
SII		696.54 ± 94.02	631.28 ± 134.28	3.120	0.002
NEU (×10^9/L)		5.97 ± 0.52	5.89 ± 1.12	0.447	0.655
PLT (×10^9/L)		184.99 ± 8.99	168.69 ± 10.77	9.323	<0.001
LYM (×10^9/L)		1.59 ± 0.12	1.58 ± 0.13	0.522	0.603
RBC (×10^9/L)		4.50 ± 0.12	4.49 ± 0.14	0.300	0.765
WBC (×10^9/L)		9.10 ± 0.12	9.09 ± 0.16	0.259	0.796
Comorbidities (types)	0	22	40	0.037	0.982
	1	24	46		
	≥2	6	12		
Length of hospital stay (days)	≤7	30	60	0.177	0.674
	>7	22	38		
Caregiver's education level	High school and below	16	33	0.130	0.718
	college and above	36	65		

Abbreviations: BT-UTI, breakthrough urinary tract infection; BMI, body mass index; LYM, lymphocytes; NEU, neutrophils; PLT, platelets; RBC, red blood cells; SII, systemic immune-inflammation index; UDR, ureteral diameter ratio; VUR, vesicoureteral reflux; WBC, white blood cells.

UTIs that occur in patients despite receiving prophylactic antibiotic treatment. Therefore, accurately predicting the risk of early BT-UTI in children with VUR is of significant importance for optimizing treatment strategies and reducing complications. This study aimed to investigate the predictive value of SII combined with UDR for early BT-UTI in children with VUR, with the hope of providing new predictive tools for clinical practices.

SII, as a comprehensive inflammatory marker, reflects the immune-inflammatory status of the body. Our binary logistic regression analysis indicated that UDR and SII were influencing factors for early BT-UTI in children with VUR, and SII was negatively correlated with LYM and positively correlated with PLT and NEU. This result suggests that the elevation of SII may be associated with an exacerbation of the body's immune-inflammatory response, which could promote bacterial adhesion and colonization on the urothelium, thereby increasing the risk of early BT-UTI. These speculations support that the increase in SII directly reflects the enhancement of the body's immune and inflammatory responses [13,14]. Due to urine reflux to the kidneys, children suffering VUR are prone to inflammation and immune responses in the kidneys and urothelium. This inflammatory response may further exacerbate the overall immune status of the body, leading to an increase in SII [15]. As mentioned above, the exacerbation of the immune-inflammatory response may promote bacterial adhesion and colonization on the urothelium. Particularly in children with VUR, urine reflux creates an optimal condition for bacterial adherence and colonization on the urothelium. This adhesion and colonization may further aggravate the body's immune-inflammatory response, setting up a vicious cycle. Furthermore, due to the exacerbation of the immune-inflammatory response and bacterial adhesion and colonization on the urothelium, the risk of early BT-UTI in children with VUR may increase. The occurrence of UTI further exacerbates the body's immune-inflammatory response, leading to a sustained increase in SII. The prognostic and predictive value of SII in various diseases has been reported previously [16]. However, there is limited

Table 2. Results of correlation analysis.

		NEU	PLT	LYM	SII	UDR
NEU	*r*	1	0.007	–0.061	0.839	0.076
	p	-	0.936	0.456	<0.001	0.352
PLT	*r*	0.007	1	0.062	0.366	0.280
	p	0.936	-	0.448	<0.001	0.001
LYM	*r*	–0.061	0.062	1	–0.418	0.033
	p	0.456	0.448	-	<0.001	0.689
SII	*r*	0.839	0.366	–0.418	1	0.162
	p	<0.001	<0.001	0.000	-	0.047
UDR	*r*	0.076	0.280	0.033	0.162	1
	p	0.352	0.001	0.689	0.047	-

Table 3. Binary logistic regression analysis of influencing factors.

Factor	B	SE	Wald	*p*	Exp (B)	95% CI	
						Lower limit	Upper limit
UDR	0.158	0.033	23.367	<0.001	1.171	1.099	1.249
SII	1.669	0.319	27.400	<0.001	5.306	2.841	9.912
Reflux grade	-	-	7.020	0.071	-	-	-
Reflux grade (1)	0.010	0.978	<0.001	0.992	1.010	0.148	6.873
Reflux grade (2)	1.309	0.904	2.096	0.148	3.704	0.629	21.797
Reflux grade (3)	1.344	0.951	1.996	0.158	3.835	0.594	24.752
Constant	–11.728	2.160	29.482	<0.001	<0.001	-	-

Abbreviations: CI, confidence interval; SE, standard error.

Table 4. Results of ROC curve analysis.

Index	AUC	SE	95% CI	Youden	Sensitivity	Specificity	Cutoff value
SII	0.648	0.044	0.561–0.735	0.33	98.1	34.7	548.69
UDR	0.814	0.034	0.747–0.881	0.46	96.2	50.0	0.43
Combined index	0.832	0.032	0.768–0.895	0.53	90.4	62.2	-

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

analysis in studies related to VUR patients. The results of this study further expand the application of SII in the field of pediatrics, especially in the prediction of early BT-UTI in children with VUR.

UDR, as a parameter reflecting the morphology of the ureter, was found in this study to have high value in predicting early BT-UTI in children with VUR. UDR is unrelated to NEU and LYM, and positively correlated with PLT. This result suggests that changes in UDR may be related to anatomical and functional abnormalities of the ureter, which could lead to urine retention in the ureter, increasing the risk of bacterial growth and UTI. Alterations in ureter morphology play a crucial role in the occurrence and progression of VUR. The results of this study support this notion and further indicate that UDR can serve as a useful indicator for predicting early BT-UTI in children with VUR, on top of its rather simple and non-invasive measurement, as well as feasibility for widespread application in clinical practice.

The results of this study demonstrate that the combined use of SII and UDR in predicting early BT-UTI in children with VUR yielded an area under the ROC curve of 0.832, with a sensitivity of 90.4% and specificity of 62.2%. The closer the area under the ROC curve is to 1, the more accurate the predictive model. Therefore, these results suggest that the combination of SII and UDR holds significant predictive value and can serve as an important reference for clinical decision-making. Additionally, the model's high sensitivity indicates good performance in predicting positive cases. One possible reason for this could be that the SII, as a comprehensive inflammatory marker, can reflect the immune-inflammatory status of the body. An increase in SII may provide an indication of the body's immune-inflammatory status in response to bacterial infections, aiding in identifying VUR children at high risk of infection. UDR directly reflects anatomical changes in the ureter, which could lead to urine retention and provide an environment for bacterial growth [17]. Thus, UDR changes indirectly reflect the severity of VUR and the risk of UTI. The combined use of SII and UDR considers both the body's immune-inflammatory status and ureteral morphological changes, enabling a comprehensive assessment of the risk of early

BT-UTI in children with VUR. Sensitivity is a measure of a predictive model's ability to identify positive cases. In this study, the sensitivity of the combined SII and UDR model was 90.4%, indicating the model's ability to accurately identify the majority of VUR children with early BT-UTI. High sensitivity of a predictive model is crucial for clinical decision-making as it helps physicians promptly identify high-risk patients for infection, enabling timely intervention to reduce the incidence of UTIs and associated complications. Specificity measures a predictive model's ability to identify negative cases. In this study, the specificity of the combined SII and UDR model was 62.2%, which surpasses the average. Improving specificity may require further optimization of the predictive model, like introducing more biomarkers or clinical indicators, or refining the model's algorithm to enhance its accuracy.

The results of this study hold significant implications for optimizing treatment strategies for children with VUR and reducing complications. By predicting the risk of early BT-UTI in children with VUR, more accurate antibiotics-based preventive strategies can be designed to avoid unnecessary drug exposure and potential medication side effects. Moreover, for high-risk patients, physicians can implement more proactive monitoring and treatment measures to promptly detect and manage UTIs, thereby reducing kidney damage and the occurrence of long-term complications.

Despite the promising results achieved, this research is not without limitations. First of all, this retrospective study may be prone to selection bias and information bias. Secondly, the relatively small sample size (only 150 patients) may limit the statistical power and robustness of the results, thus affecting the generalization of the conclusions to a wider population. In addition, the lack of external or prospective validation of predictive models combining SII and UDR leaves uncertainty in the reliability and generalization of the model. Finally, although the combined model is highly sensitive, it has moderate specificity, which may lead to a higher false positive rate. The impact of this trade-off on clinical practice has not been thoroughly discussed, especially the possible consequences for patient management. Future research can further expand the sample size and carry out prospective studies to verify the reliability and accuracy of the results of this study. At the same time, other possible prediction factors can be explored and a more complete predictive model can be established. In addition, basic research can also be carried out to deeply explore the mechanism of SII and UDR in the occurrence and development of VUR and UTI to provide more in-depth theoretical support for clinical practice.

Conclusions

In conclusion, both SII and UDR have high predictive value for early BT-UTI in VUR patients, and their combined application can further enhance the accuracy of prediction. The findings of this study provide new insights and methods for optimizing treatment plans for children with VUR and reducing complications, which holds significant clinical importance and promising application prospects. Future researches can further validate and refine the results of this study, providing more robust evidence to support the application of the combined index in clinical practices.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

XXC and YC designed the research study; WHZ performed the research; XXC and XYT collected and analyzed the data. FC and XJY conducted experiments, provided design consultation, and drafted the manuscript. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Medical Ethics Committee of the Shanghai Children's Hospital, of Medicine Shanghai Jiao Tong approved the study (2024R165-E01). Informed consent was obtained from the patients or their families after having been fed with the information about the study.

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Conflict of Interest

The authors declare no conflict of interest.

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