Original Article

Risk factors and predictive models for early recurrent intussusception in children: a retrospective cohort study

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Background: Early recurrent intussusception (ERI) in children is common and seriously affects the physical and mental health of the children. There are few reports discussing risk factors for ERI in children, and this study aims to identify risk factors for ERI in children and build predictive models.

Methods: We conducted a retrospective study of 787 children with no relapse intussusception (NRI) and 82 children with ERI between January 2011 and December 2021. Univariate and multifactorial stepwise logistic regression analysis was used to analyze the correlation between 11 factors and ERI, to determine the independent risk factors for ERI in children. The prediction model was established by independent risk factors and then verified.

Results: Age, vomiting, bloody stools, and monocyte ratios were independently correlated with the composite endpoint (P<0.05). A nomogram was constructed and a calibration curve was plotted, using independent risk factors. Based on the disease's diagnostic score, the predictive model's performance was validated by using logistic regression receiver operating characteristic (ROC) curve detection, with area under the curve (AUC) value of 0.883 [95% confidence interval (CI): 0.846–0.920], and the calibration curve was close to the ideal diagonal line. In addition, the decision curve analysis (DCA) showed that the model had significant net benefits.

Conclusions: Independent risk factors for ERI in children are age, vomiting, bloody stool, and monocyte ratio. Children older than 1 year in age, who lacked vomiting and bloody stool symptoms, and who exhibited an elevated ratio of monocytes were more likely to relapse early. The predictive model constructed herein can predict the early recurrence of children with ERI, providing a reference for clinicians' individualized judgments.

Keywords: Intussusception; early recurrent; monocyte ratio; intestinal flora

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Introduction

Intussusception is one of the most common abdominal emergencies in children. Recurrent intussusception refers to the recurrence of intussusception in children who have been successfully reset by enema therapy or surgery. Recurrence of intussusception is fairly common regardless of the method of reduction (1), with incidence ranging from 2% to 20% (2-5).

Intussusception recurrence can be divided into early recurrent intussusception (ERI) and late recurrence intussusception (LRI). Currently, there is no clear time limit for what early recurrence is. Some surveys found that nearly 50% of recurrent intussusception occurred within the first week after the first reduction (3), known as ERI, while others considered recurrence within 24 hours to be an early recurrence, on the other hand, some researchers still defined early recurrence as 48 or 72 hours (6-9). Research by Wang *et al.* has shown that 92.1% of early relapses occur within 48 hours (10).

Some cases of intussusception can recur several times in a short period, which seriously affects the physical and mental health of the patient. Previous studies have failed to identify consistent risk factors for intussusception recurrence, and risk factors for ERI in children have rarely been reported. Therefore, we attempted to investigate the risk factors for ERI in children and build predictive models to help with the individualized judgment of clinicians. We present this article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-269/rc).

Highlight box

Key findings

- Independent risk factors for early recurrent intussusception (ERI) in children are age, vomiting, bloody stool, and monocyte ratio. By adding the scores for each selected variable in the nomogram we could estimate the likelihood of ERI.

What is known and what is new?

- Previous studies on recurrent intussusception have found that age and vomiting are risk factors for recurrent intussusception.
- We found that age, vomiting, bloody stool, and monocyte ratio are independent risk factors for ERI in children. We built a visualized and personalized nomogram model based on the abovementioned factors for the early prediction of ERI.

What is the implication, and what should change now?

- We found that monocytes are an independent risk factor for ERI. Based on the relationship between intestinal flora and monocytes, the hypothesis of the correlation between intestinal flora and monocytes and intussusception recurrence was proposed.

Methods

Study design and population

The purpose of this study was to retrospectively investigate the data on intussusception in children admitted to the First Affiliated Hospital of Shantou University Medical College, China. This retrospective study has been registered with the Chinese Clinical Trial Registry (No. ChiCTR2200063862). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College (No. B-2022-163). The informed consent was waived for this retrospective study.

Our study cohort was comprised of 983 children admitted to the First Affiliated Hospital of Shantou University Medical College from January 2011 to December 2021 due to pediatric intussusception. The inclusion criteria were as follows: (I) a previous diagnosis of intussusception that had been successfully reduced by enema therapy or surgery; (II) a confirmed diagnosis of recurrent intussusception based on the patient's clinical manifestations, physical examination, color ultrasound, and other tests, with other causes excluded; and (III) the recurrence having occurred within 48 hours of the first occurrence. The exclusion criteria were as follows: incomplete clinical data. After applying all the inclusion criteria and exclusion criteria, the final study cohort consisted of 869 cases.

Data collection

The data collected included 11 factors before treatment, including the child's sex, age, onset quarter, duration of symptoms, clinical manifestations (abdominal pain or crying, vomiting, bloody stool, fever), white blood cells (WBCs), lymphocyte ratio, and monocyte ratio.

Definitions

Existing articles have different definitions of early recurrence time. Moreover, children treated for intussusception in this study were generally discharged after 48 hours of observation following reduction. Thus,

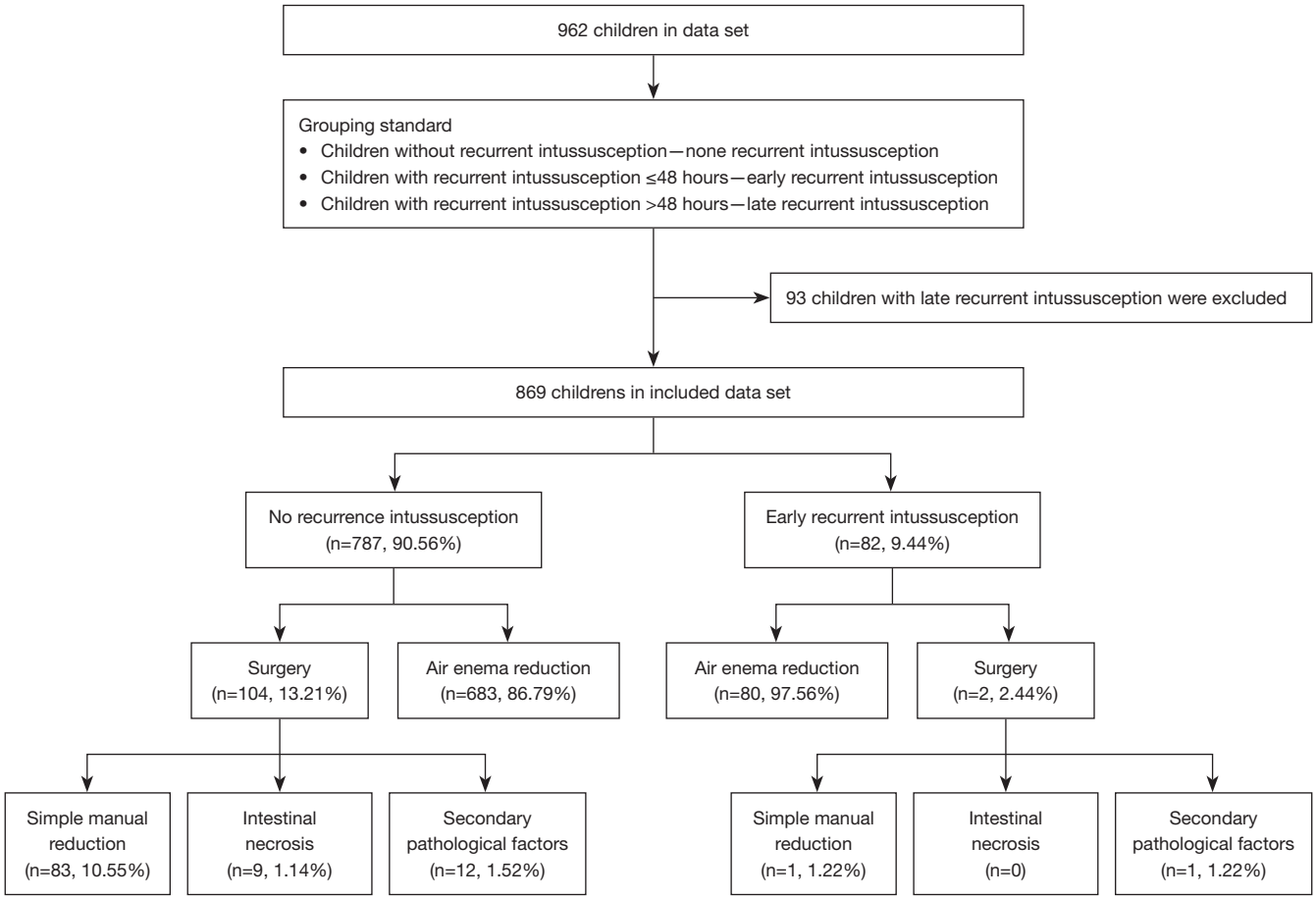

Figure 1 Specific groups and treatment methods for children with intussusception.

this study defined recurrence within 48 hours as early recurrence. Referring to the "Reference intervals of blood cell analysis for children" (11), we define WBCs, lymphocyte ratio, and monocyte ratio as high, normal, and low respectively.

Statistical analysis

Clinical data from the ERI group and the no relapse intussusception (NRI) group were statistically analyzed, and categorical variables were expressed in terms of frequency and percentage. The χ^2 test or Fisher's exact test was used for univariate analysis of related variables. Statistically significant risk factors in the univariate analysis were then subjected to logistic multifactorial analysis of independent risk factors for ERI (12). Patients were randomly divided into a training set and a validation set in a 7:3 ratio, which was used for model development and validation, respectively. Based on the results of logistic multivariate analysis, we constructed a nomogram to predict ERI. We plotted a calibration curve on this diagram. Finally, we used the receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) to detect the performance of the predictive model. $P<0.05$ was considered statistically significant.

All analyses were performed with the statistical software packages R (https://www.r-project.org/; The R Project for Statistical Computing, Vienna, Austria) and Free Statistics software version 1.3.

Results

General characteristics

The characteristics of patients in each study group are shown in *Figure 1*. Among the children who did not relapse, 104 (13.21%) underwent surgical treatment, 83 (10.55%)

Table 1 Age distribution of children with intussusception

Age	Intussusception (n=869)	NRI (n=787, 90.56%)	ERI (n=82; 9.44%)
<1 year old	312 (35.90)	309 (39.26)	3 (3.66)
≥1 and <2 years old	194 (22.32)	175 (22.24)	19 (23.17)
≥2 and <3 years old	159 (18.30)	124 (15.76)	35 (42.68)
≥3 years old	204 (23.48)	179 (22.74)	25 (30.49)

Data are presented as n (%). NRI, none recurrent intussusception; ERI, early recurrent intussusception.

underwent simple manual reduction, and 9 children (1.14%) had intestinal necrosis; among the children with early recurrence, 2 (2.44%) underwent surgical treatment, 1 (1.22%) underwent simple manual reduction, and 0 children had intestinal necrosis. Children with early recurrence had a smaller probability of undergoing simple manual reduction or experiencing intestinal necrosis. *Table 1* shows the age distribution of the 869 children with intussusception included in this study. Intussusception and NRI were more likely to occur in children <1 year old of age, and the incidence of both decreased with age. ERI tended to occur in children aged ≥2 and <3 years old. The incidence of ERI increased with age in children aged <3 years old and decreased in children ≥3 years old.

Univariate analysis

Of the 869 children with intussusception, 82 had an ERI, and 787 had NRI. Univariate analysis of 11 factors showed that age, abdominal pain or crying, vomiting, bloody stools, and monocyte ratio were potential risk factors for ERI (P<0.05) (*Table 2*). Compared with the NRI group, children with ERI tended to be older than 1 year old, and had more abdominal pain or crying symptoms, less vomiting and bloody stool, and higher monocytes.

Multivariate analysis

Multivariate analysis showed that age [odds ratio (OR), 7.67; 95% confidence interval (CI): 2.27–25.89; P=0.001], vomiting (OR, 0.17; 95% CI: 0.09–0.32; P<0.001), bloody stool (OR, 0.14; 95% CI: 0.03–0.63; P=0.01), and monocyte ratio (OR, 9.52; 95% CI: 2.14–42.25; P=0.003) were independently associated with the clinical endpoints. Age, vomiting, bloody stool, and monocyte ratio were independent risk factors for ERI in children (*Table 3*). The results of the multivariate analysis are presented in a logistic regression forest plot (*Figure 2*).

Establishment and validation of predictive models

A nomogram (*Figure 3*) was constructed based on four independent predictors of ERI: age, vomiting, bloody stool, and monocyte ratio. By adding the scores for each selected variable in the nomogram we could estimate the likelihood of ERI in a single patient.

Predictive accuracy and net benefit of the nomogram

The calibration curve showed the relationship between the risk of ERI in children and the actual risk of occurrence. In our cohort, the calibration curve was close to the ideal diagonal (*Figure 4*). Based on the diagnostic score of the disease, the performance of the predictive model was detected using a ROC curve with area under the curve (AUC) value of 0.883 (95% CI: 0.846–0.920) (*Figure 5*). In addition, DCA showed significant net benefits for the predictive model (*Figure 6*). These data show that our nomogram has important potential in clinical decision-making.

Discussion

In previous studies, the incidence of ERI in children ranged from 5% to 12.5% (10,13,14), in agreement with this range, the incidence of pediatric ERI in this study was 9.44%. The mortality rate of intussusception depends heavily on the availability of appropriate treatment in a timely manner, ranging from less than 1% in developed countries to as high as 10% in low-income countries (15). ERI in children recurs within a very short period of time. Early discharge followed by readmission can delay treatment and increase the hassle of traveling back and forth, causing problems for doctors and parents. Early prediction of ERI is therefore important in determining the length of hospital stay and reducing mortality from intestinal obstruction. Although modern medicine has made great progress, there is still insufficient attention to the recurrence of intussusception.

Table 2 Univariate analysis of risk factors for ERI in children

Factors	Total (n=869)	NRI (n=787, 90.56%)	ERI (n=82; 9.44%)	P	Chi-squared
Season of one				0.947	0.365
The first season	203 (23.4)	185 (23.5)	18 (22.0)		
The second season	216 (24.9)	194 (24.7)	22 (26.8)		
The third season	234 (26.9)	211 (26.8)	23 (28.0)		
The fourth season	216 (24.9)	197 (25.0)	19 (23.2)		
Gender				0.753	0.099
Male	591 (68.0)	537 (68.2)	54 (65.9)		
Female	278 (32.0)	250 (31.8)	28 (34.1)		
Age				<0.001	39.375
<1 year old	312 (35.9)	309 (39.3)	3 (3.7)		
≥1 year old	557 (64.1)	478 (60.7)	79 (96.3)		
Duration of symptoms				0.574	0.316
≤12 hours	372 (42.8)	334 (42.4)	38 (46.3)		
>12 hours	497 (57.2)	453 (57.6)	44 (53.7)		
Abdominal pain cry				0.023	5.163
No	133 (15.3)	128 (16.3)	5 (6.1)		
Yes	736 (84.7)	659 (83.7)	77 (93.9)		
Emesis				<0.001	72.145
No	320 (36.8)	254 (32.3)	66 (80.5)		
Yes	549 (63.2)	533 (67.7)	16 (19.5)		
Bloody stools				<0.001	34.022
No	595 (68.5)	515 (65.4)	80 (97.6)		
Yes	274 (31.5)	272 (34.6)	2 (2.4)		
Temperature				0.083	3.006
≤38 ℃	670 (77.1)	600 (76.2)	70 (85.4)		
>38 ℃	199 (22.9)	187 (23.8)	12 (14.6)		
WBCs				0.557	Fisher
Low	5 (0.6)	5 (0.6)	0 (0.0)		
Normal	340 (39.1)	303 (38.5)	37 (45.1)		
High	524 (60.3)	479 (60.9)	45 (54.9)		
Lymphocyte ratio				0.370	1.986
Low	223 (25.7)	200 (25.4)	23 (28.0)		
Normal	491 (56.5)	442 (56.2)	49 (59.8)		
High	155 (17.8)	145 (18.4)	10 (12.2)		
Monocyte ratio				<0.001	60.009
Low	63 (7.2)	61 (7.8)	2 (2.4)		
Normal	584 (67.2)	554 (70.4)	30 (36.6)		
High	222 (25.5)	172 (21.9)	50 (61.0)		

Data are presented as n (%). ERI, early recurrent intussusception; NRI, none recurrent intussusception; WBC, white blood cell.

Table 3 Multivariate analysis of risk factors for ERI in children

Factors	OR (95% CI)	P
Age		
<1 year old	1 (ref)	
≥1 year old	7.67 (2.27–25.89)	0.001
Abdominal pain cry		
No	1 (ref)	
Yes	0.54 (0.18–1.59)	0.263
Emesis		
No	1 (ref)	
Yes	0.17 (0.09–0.32)	<0.001
Bloody stools		
No	1 (ref)	
Yes	0.14 (0.03–0.63)	0.01
Monocyte ratio		
Low	1 (ref)	
Normal	1.6 (0.36–7.14)	0.536
High	9.52 (2.14–42.25)	0.003

ERI, early recurrent intussusception; OR, odds ratio; CI, confidence interval; ref, reference.

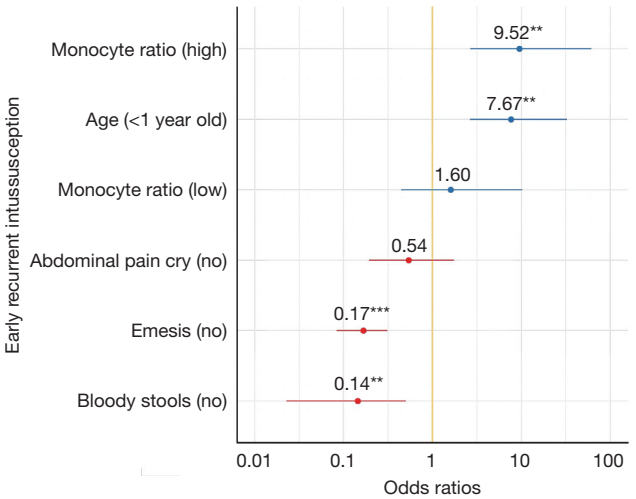

Figure 2 Logistic regression forest plot. The blue line represents OR >1 and the red line represents the OR <1. **, 0.001≤P<0.05; ***, P<0.001. OR, odds ratio.

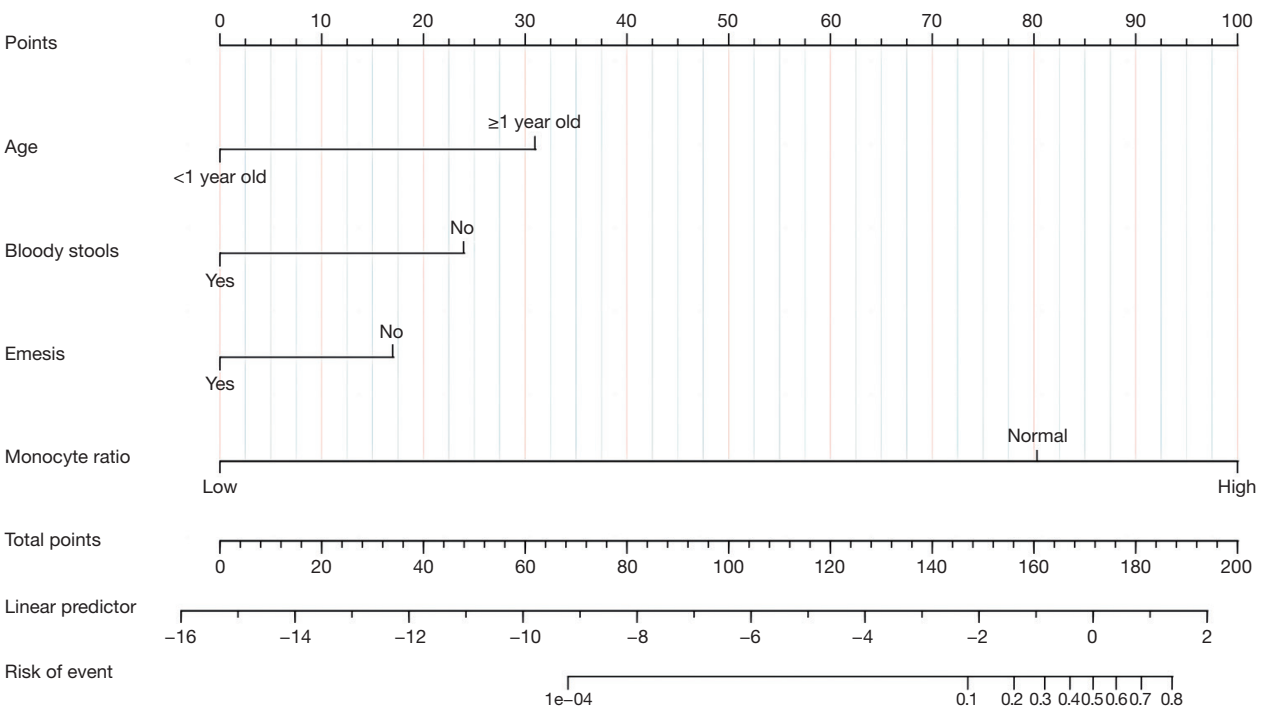

Figure 3 Nomogram predicting the occurrence of ERI in children. ERI, early recurrent intussusception.

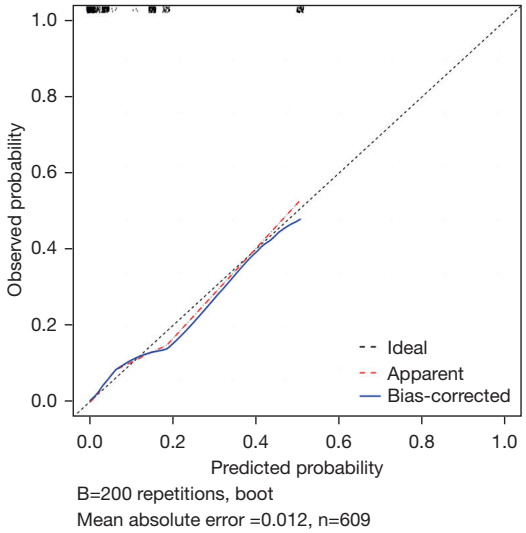

Figure 4 Calibration curve showing the consistency of the risk of ERI in children with the actual risk of occurrence. ERI, early recurrent intussusception.

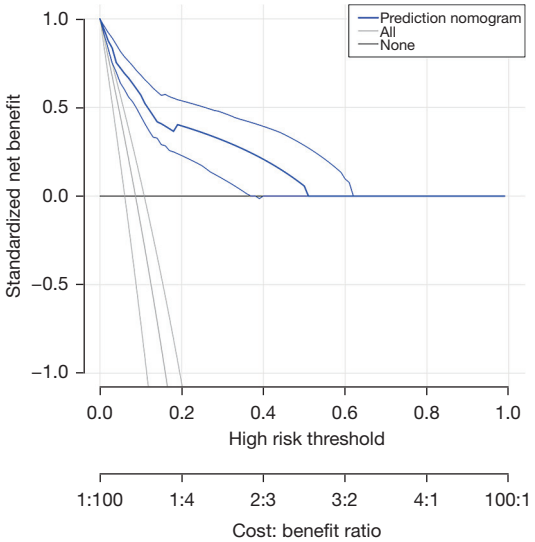

Figure 6 DCA in the prediction of ERI in children. DCA, decision curve analysis; ERI, early recurrent intussusception.

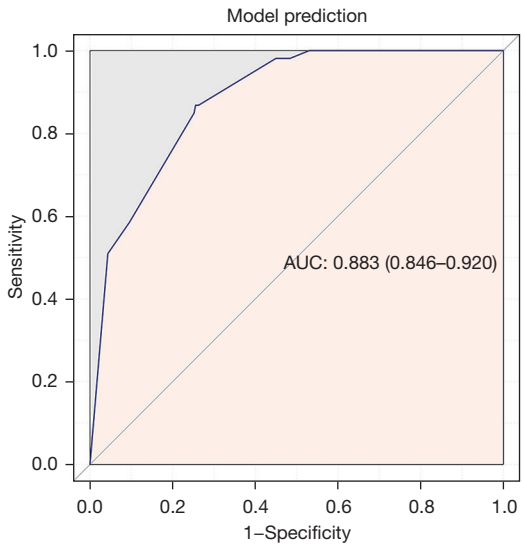

Figure 5 ROC curve of the established predictive model. The AUC of this model was 0.883 (95% CI: 0.846–0.920). AUC, area under the curve; ROC, receiver operating characteristic.

There has been no consistent report on the recurrence of intussusception in previous studies, and the characteristics of ERI are rarely reported.

Our study retrospectively analyzed 11 factors—including sex, age, onset quarter, duration of symptoms, clinical manifestations (abdominal pain or crying, vomiting, bloody stool, fever), WBCs, lymphocyte ratio, and monocyte ratio before treatment in 82 children with ERI and 787 children with NRI. The results of this study show that age, vomiting, bloody stool, and monocyte ratio are independent risk factors for relapse of intussusception in children.

Age >1 year has been shown to be a risk factor for early recurrence (16,17), and our findings are consistent with this. In this study, we found that ERI incidence in children aged 0–3 years increased with age, but then decreased in children older than 3 years. Research by Stewart *et al.* has shown that the development of the pediatric gut microbiota goes through three distinct stages: the developmental stage before 14 months of age, the transitional stage of 15 to 30 months of age, and the stable stage of 31 to 46 months of age (18). During this process, the composition of the microbiome changes rapidly until about the age of 3 years when the diversity and complexity of the microbiome resemble that of adulthood (19-21). This coincidental timing begs the question of whether the occurrence of pediatric ERI is related to the transformation of the intestinal flora. A study has shown that the gut microbiota is essential for the development of gut-associated lymphoid tissue, including Peyer's plaque and mesenteric lymph nodes, and contributes to the local and systemic immune systems (22). In intussusception reduction surgery, enlarged Peyer's plaques and mesenteric lymph nodes are common (10). Therefore, we speculate that, from the age of 0–3 years,

when the pediatric intestinal flora is in a period of dramatic change, the development of Peyer's plaque and mesenteric lymph nodes can be easily perturbed, causing Peyer's spots and mesenteric lymph nodes to enlarge and affecting the systemic immune system. Enlargement of these structures can disrupt intestinal peristalsis patterns, leading to ERI. After the age of 3 years, the intestinal flora tends to stabilize, and the incidence of pediatric ERI gradually decreases.

Vomiting and bloody stool are common clinical symptoms of intussusception in children, often caused by intestinal obstruction, ischemia, and necrosis. In previous studies of ERI, children with early intussusception were found to have a significantly lower rate of vomiting and bloody stool than children who did not have a recurrence (14,23). In the current study, vomiting and bloody stool were protective factors for pediatric ERI, and children with ERI exhibited less vomiting and fewer bloody stools. We hold the opinion that vomiting and bloody stools are unlikely to manifest in the early stage of intussusception onset when the irregular activity of the intestine is more intense and more likely to lead to ERI.

Our results show that the monocyte ratio is an independent risk factor for pediatric ERI and that children with a high monocyte ratio are more likely to relapse early. Monocytes are circulating WBCs that are essential for immune defense against viral, bacterial, and fungal infections (24,25). Since there is no clear starting point for intussusception, the etiology of primary intussusception remains inconclusive. At present, the main causes associated with primary intussusception in children are anatomical factors, viral infections, gastrointestinal dysfunction, and weather factors (26-28). Viral infection causes mesenteric lymphadenopathy and an elevated monocyte ratio, which may explain the elevated monocyte ratio in pediatric ERI patients. The intestinal flora is closely related to the immune status of the gut. In a study of type 1 diabetes (T1D), a significant T1D-specific inflammatory state was found, mainly manifested by increased monocyte/macrophage lineage infiltration. The expression of T1D inflammation-specific genes was associated with the abundance of specific bacteria in the duodenum (29). Do changes in the microbiome in the gut affect the proportion of monocytes? Increased intestinal mucosal macrophage infiltration may damage the intestinal mucosal barrier (29). The intestinal microbiota can translocate through the damaged intestinal mucosa to Peyer's plaque and mesenteric lymph nodes, causing enlargement of Peyer's plaque and mesenteric lymph nodes (30). Enlarged Peyer's spots and mesenteric lymph nodes could also be seen in children with intussusception who required a surgical reduction in this study. Therefore, we propose that the intestinal flora of children with ERI changes, causing an increase in intestinal monocytes and macrophages, resulting in damage to the intestinal mucosal barrier. The gut microbiome affects the systemic immune system through the damaged intestinal mucosal barrier so that monocytes further increase or reach Peyer's plaque and mesenteric lymph nodes, causing Peyer's spots and mesenteric lymph nodes to enlarge, and eventually cause ERI. This is consistent with our inference above regarding the development of the gut microbiota as a function of age, but the specific mechanisms require further study.

Based on the independent risk factors for ERI found in this study, we established a predictive model for pediatric ERI. Age >1 year is positively correlated with the onset of pediatric ERI, a high proportion of monocytes is the most significant independent risk factor predicting ERI risk in children, and vomiting and blood are protective factors for pediatric ERI. We plotted a calibration curve that shows that the actual probability is substantially consistent with the predicted probability. At the same time, we used the ROC curve to detect the performance of the predictive model with an AUC value of 0.883 (95% CI: 0.846–0.920), and the calibration curve was close to the ideal diagonal line. In addition, the DCA showed that the model had significant net benefits. These results show that our predictive models have good accuracy and stability.

However, our study had several limitations. First, in this retrospective study, potentially meaningful predictors such as "ultrasonography (USG), C-reactive protein, birth pattern, birth weight, feeding pattern, antibiotic use, etc." were not evaluated due to a lack of data. In further studies, we will evaluate more potential indicators and build more accurate prediction models for pediatric ERI based on clinical features. Second, because the study is retrospective, there is inevitably some degree of internal bias. Third, there is no clear cut-off point for what constitutes an early relapse. Research by Wang *et al.* suggested that 92.1% of early recurrences occur within 48 hours (10), and in this study children with intestinal obstruction were observed for 48 hours after successful reduction and then discharged, so a recurrence within 48 hours was defined as an early recurrence. Large studies are still needed to define ERI and LRI in intussusception. Fourth, only one central set of data was collected for analysis, so we will seek external validation assessments in multicenter studies.

Conclusions

We found that age, vomiting, bloody stool, and monocyte ratio are independent risk factors for the occurrence of pediatric ERI. Children older than 1 year, who do not exhibit vomiting or bloody stool, and who do exhibit an increased ratio of monocytes, are at a higher risk for ERI. Our predictive model has the potential to provide individualized risk estimates for pediatric ERI for children with intussusception. And it can provide a theoretical basis for the length of stay of the child.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-269/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-269/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College (No. B-2022-163). The informed consent was waived for this retrospective study.

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