Risk factors for intussusception in children with Henoch-Schönlein purpura: A case-control study

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Abstract

BACKGROUND
The etiology of Henoch-Schönlein purpura (HSP) with intussusception remains undefined.

AIM
To investigate the risk factors for intussusception in children with HSP and gastrointestinal (GI) involvement.

METHODS
Sixty children with HSP and concomitant intussusception admitted to the Beijing Children’s Hospital of Capital Medical University between January 2006 and December 2018 were enrolled in this study. One hundred pediatric patients with HSP and GI involvement but without intussusception, admitted to the same hospital during the same period, were randomly selected as a control group. The baseline clinical characteristics of all patients, including sex, age of onset, duration of disease, clinical manifestations, laboratory test results, and treatments provided, were assessed. Univariate and multiple logistic regression analyses were performed to identify possible risk factors.

RESULTS
The 60 children in the intussusception group comprised 27 girls (45%) and 33 boys (55%) and the 100 children in the non-intussusception group comprised 62 girls (62%) and 38 boys (38%). The median age of all patients were 6 years and 5 mo. Univariate and multiple regression analyses revealed age at onset, not receiving glucocorticoid therapy within 72 h of emergence of GI symptoms, hematochezia, and D-dimer levels as independent risk factors for intussusception in children with HSP (P < 0.05).

CONCLUSION
The four independent risk factors for intussusception in pediatric HSP with GI involvement would be a reference for early prevention and treatment of this potentially fatal disease.

Key Words: Henoch-Schönlein purpura; Intussusception; Gastrointestinal; Risk factors; Children; Logistic regression analysis

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Core Tip: Intussusception has an incidence of about 5% in Henoch-Schönlein purpura (HSP), and is a common cause of acute surgical abdomen in the affected children. There is limited research on risk factors for intussusception in children with HSP. Age at onset below 6 years, not receiving glucocorticoid therapy within 72 h of onset of gastrointestinal (GI) symptoms, hematochezia, and increased D-dimer levels are independent risk factors for intussusception in children with HSP and GI involvement.

INTRODUCTION
Henoch-Schönlein purpura (HSP), a common leukocytoclastic vasculitis involving the capillaries and arterioles, is mediated by immune complexes[1]. HSP is one of the most common childhood vasculitides, and approximately two thirds of children with HSP have gastrointestinal (GI) symptoms[2]. Children with HSP and GI involvement may exhibit concomitant acute abdominal symptoms, including GI bleeding, intussusception, intestinal obstruction, intestinal necrosis, intestinal perforation, pancreatitis, and appendicitis, all of which require surgical intervention[3]. Severe GI involvement may be fatal and associated with renal involvement[4]. Few reports have assessed HSP and concomitant intussusception in children. However, it was reported that the typical age of onset of intussusception in HSP with GI involvement is about 6 years old, which is much older than that of primary intussusception (4–12 mo)[5]. Meanwhile, it is known that intussusception has an incidence of about 5% in HSP cases, and represents the most common reason for acute surgical abdomen in these children[6]. Intussusception can be fatal if not diagnosed and treated in a timely manner[7]. However, few reports have assessed the etiology of intussusception in children with HSP due to its low clinical incidence. In particular, the risk factors for intussusception in children with HSP are largely unknown. Therefore, the aim of this study was to identify risk factors for the development of intussusception in children with HSP. We found that age at onset below 6 years, not receiving glucocorticoid therapy within 72 h of onset of GI symptoms, hematochezia, and high D-dimer levels independently predict intussusception in pediatric HSP with GI involvement. These data may serve as a reference for early prevention and treatment of this potentially fatal disease.

MATERIALS AND METHODS
Study population and design
This retrospective study assessed patients with HSP and concomitant intussusception admitted to the Beijing Children’s Hospital of Capital Medical University between January 2006 and December 2018. Meanwhile, individuals with HSP and GI involvement but without intussusception, admitted to the same hospital during the same period, were randomly selected as a control group.
The inclusion criteria were: (1) Age from 1 to 17 years old; and (2) Diagnosis of HSP and GI symptoms. The exclusion criterion were: (1) Incomplete clinical data; and (2) Patients with severe heart, brain, liver, kidney, lung, and hematopoietic system diseases.

The study protocol was approved by the Institutional Review Board of Beijing Children’s Hospital, Capital Medical University, China (approval number IEC C-008-A08-V.05.1). The requirement for informed consent was waived because of the retrospective nature of the research and data anonymity.

Data collection and definitions
The baseline clinical characteristics of all patients with HSP, including sex, age at onset, disease duration, clinical manifestations, laboratory test results, treatments, and follow-up duration, were collected.

Intussusception refers to the intussusception or retraction into the lumen of a segment of the intestine\[8\]. In this case, the related mesentery is pulled and compressed in the varus segment, resulting in congestion and edema, which causes a series of clinical symptoms. Intussusception is the second most common acute abdominal ailment in children after appendicitis\[9\]. The typical triad of intussusception includes abdominal pain, vomiting, and bloody stools, occurring in less than half of cases\[7\]. In case of clinical suspicion of intussusception, abdominal ultrasound should be performed for confirmation. The sensitivity and specificity of abdominal ultrasound in the diagnosis of intussusception are 100% and 80%-100%, respectively \[9\].

All patients with HSP met the diagnostic criteria jointly developed in 2010 by European League Against Rheumatism and Paediatric Rheumatology International Trials Organization\[10\]. Abdominal ultrasonography in a patient with concomitant intussusception revealed typical “concentric ring signs” or “sleeve” like changes suggestive of intussusception. GI involvement in HSP was defined as the presence of any of the following findings: Acute diffuse abdominal pain, intussusception, and GI bleeding.

Statistical analysis
Normally distributed continuous data are expressed as the mean ± SD, and non-normally distributed ones are expressed as median and interquartile ranges (Q1 and Q3). Categorical data are expressed as n (%). Categorical variables were compared by the Chi-square test. Variables with \(P < 0.05\) in univariate analysis were entered into stepwise multiple logistic regression analysis. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and \(P\) values, for each model. Statistical analyses were performed with SPSS version 22.0 (IBM corporation, Armonk, NY, United States). \(P < 0.05\) was considered statistically significant.

RESULTS

Clinical characteristics of the included children with HSP and GI involvement
There were a total 160 children with HSP and GI involvement in this study. The 60 children in the intussusception group comprised 27 girls (45%) and 33 boys (55%); the 100 children in the non-intussusception group comprised 62 girls (62%) and 38 boys (38%). The mean age of patients in this study was 6.6 ± 2.0 years old, and the age at disease onset was 6 years and 5 mo, ranging from 2.5 to 12 years old. Disease durations were 0.5-54.0 d (median of 5.0 d). One hundred and thirty-seven (85.7%) patients were experiencing a first episode of HSP. No patient in this cohort had a history of intussusception.

At baseline, there were statistically significant between-group differences in age at onset \(P < 0.001\), disease duration \(P = 0.02\), first disease episode status \(P = 0.017\), and whether glucocorticoid therapy was received within 72 h of emergence of GI symptoms \(P < 0.001\). There were no statistically significant between-group differences in sex distribution or GI tract malformation rate \(P > 0.05\); Table 1).

Regarding symptoms, statistically significant differences were observed in vomiting and hemaatochezia rates between the two groups \(P < 0.001\), whereas hematemesis rates were not significantly different \(P > 0.05\) (Table 1).

Clinical tests showed a statistically significant difference in white blood cell count \(P = 0.014\) and D-dimer levels \(P < 0.001\) between the study groups, but not in neutrophil count, platelet count, C-reactive protein levels, or erythrocyte sedimentation rate \(P > 0.05\); Table 1).
## Table 1 Baseline patient characteristics

| Variable                                                                 | Intussusception group (n = 60) | Non-intussusception group (n = 100) | P value |
|--------------------------------------------------------------------------|-------------------------------|-----------------------------------|---------|
| Sex, n (%)                                                               |                               |                                   | 0.383   |
| Male                                                                     | 33 (55.0)                     | 62 (62.0)                         |         |
| Female                                                                   | 27 (45.0)                     | 38 (38.0)                         |         |
| Age at onset, n (%)                                                      |                               |                                   | < 0.001 |
| < 6 yr                                                                   | 27 (45.0)                     | 9 (9.0)                           |         |
| ≥ 6 yr                                                                   | 33 (55.0)                     | 91 (91.0)                         |         |
| Duration of disease (d), n (%)                                           |                               |                                   | 0.02    |
| ≤ 28                                                                     | 58 (96.7)                     | 85 (85.0)                         |         |
| > 28                                                                     | 2 (3.3)                       | 15 (15.0)                         |         |
| First episode, n (%)                                                     |                               |                                   | 0.017   |
| Yes                                                                      | 57 (95.0)                     | 80 (80.0)                         |         |
| No                                                                       | 3 (5.0)                       | 20 (20.0)                         |         |
| GI tract malformation, n (%)                                             |                               |                                   | 0.117   |
| Yes                                                                      | 3 (5.0)                       | 1 (1.0)                           |         |
| No                                                                       | 57 (95.0)                     | 99 (99.0)                         |         |
| Receiving glucocorticoid therapy within 72 h of GI symptom emergence, n (%) |                               |                                   | < 0.001 |
| Yes                                                                      | 20 (33.3)                     | 77 (77.0)                         |         |
| No                                                                       | 40 (66.7)                     | 23 (23.0)                         |         |
| Vomiting, n (%)                                                          |                               |                                   | < 0.001 |
| Yes                                                                      | 39 (65.0)                     | 27 (27.0)                         |         |
| No                                                                       | 21 (35.0)                     | 73 (73.0)                         |         |
| Hematemesis, n (%)                                                       |                               |                                   | 0.204   |
| Yes                                                                      | 7 (11.7)                      | 6 (6.0)                           |         |
| No                                                                       | 53 (88.3)                     | 94 (94.0)                         |         |
| Hematochezia, n (%)                                                      |                               |                                   | < 0.001 |
| Yes                                                                      | 33 (55.0)                     | 14 (14.0)                         |         |
| No                                                                       | 27 (45.0)                     | 86 (86.0)                         |         |
| White blood cell count, n (%)                                            |                               |                                   | 0.014   |
| < 10.0 × 10⁹/L                                                           | 21 (35.0)                     | 55 (55.0)                         |         |
| ≥ 10.0 × 10⁹/L                                                           | 39 (65.0)                     | 45 (45.0)                         |         |
| Neutrophil count, n (%)                                                  |                               |                                   | 0.085   |
| < 10.0 × 10⁹/L                                                           | 32 (53.3)                     | 67 (67.0)                         |         |
| ≥ 10.0 × 10⁹/L                                                           | 28 (46.3)                     | 33 (33.0)                         |         |
| Platelet count, n (%)                                                    |                               |                                   | 0.168   |
| < 300.0 × 10⁹/L                                                          | 11 (18.3)                     | 28 (28.0)                         |         |
| ≥ 300.0 × 10⁹/L                                                          | 49 (81.7)                     | 72 (72.0)                         |         |
| C-reactive protein level, n (%)                                          |                               |                                   | 0.072   |
| ≤ 8 mg/L                                                                 | 26 (43.3)                     | 58 (58.0)                         |         |
| > 8 mg/L                                                                 | 34 (56.7)                     | 42 (42.0)                         |         |
Eight (13.3%) individuals had intussusception reduction via air enema (one was small intestine intussusception, and the rest were ileum colon intussusception), and the rest of 48 (80.0%) patients underwent surgery. The surgeries performed were bowel resection ($n = 18$) and manual reduction ($n = 30$). The median of nested distance in intussusception was 11 cm (range, 4-40 cm), and the median of nested diameter in intussusception was 5.0 cm (range, 1.8-8.0 cm). Small bowel intussusception was the predominant type observed during surgery ($n = 29$, 60.4%) and the rest 19 (39.6%) patients had ileocolic intussusception. Among the surgically treated patients, intestinal necrosis ($n = 18$, 37.5%), intestinal perforation ($n = 2$, 4.2%), and appendicitis ($n = 7$, 14.6%) were identified. Among them, three patients were underwent appendectomy. All the 18 cases with enterectomy had their intestinal tissue samples sent for pathological biopsy (Figure 1). Pathological results mainly showed full-thickness congestion, hemorrhage, necrosis of the intestinal wall, fibrinoid necrosis of small vessel wall, and neutrophil infiltrate on the wall and around the small vessel. Some parts of the mucosal lamina propria and submucosa were highly edema. The lamina propria and submucosa were infiltrated by acute and chronic inflammatory cells, such as sheet neutrophils, eosinophils, and plasma cells (Figure 2).

**Logistic regression analysis of potential risk factors for intussusception in children with HSP**

Eight factors with $P < 0.05$ in univariate analysis were included in the logistic regression equation. Stepwise multiple regression analysis was performed to analyze risk factors for intussusception in children with HSP. The results showed that hematochezia (OR = 5.355, 95%CI = 1.809-15.852, $P = 0.002$), D-dimer levels (OR = 7.193, 95%CI = 2.507-20.640, $P < 0.001$), glucocorticoid therapy timing (OR = 0.342, 95%CI = 0.127-0.920, $P = 0.034$), and age at disease onset (OR = 0.202, 95%CI = 0.065-0.632, $P = 0.006$) were independent risk factors for intussusception in children with HSP (Table 2).

**DISCUSSION**

The etiology of HSP accompanied by intussusception remains largely unclear, although it can lead to high mortality. The present study clearly demonstrated that age at onset below 6 years, not receiving glucocorticoid therapy within 72 h of onset of GI symptoms, hematochezia, and high Ddimer levels independently predict intussusception in pediatric HSP with GI involvement.

As shown above, median age at disease onset was 6 years and 5 mo, which is consistent with previous findings[4]. In addition, logistic regression analysis suggested that age at disease onset below 6 years was an independent risk factor for intussusception in children with HSP. This finding corroborates a previous study reporting that age under 7 years was the most common onset age in HSP with concomitant intussusception[4]. HSP tends to occur at 4-6 years of age[11,12], and children with HSP at younger ages may have more serious clinical process[13], which may be related to the fact that HSP children under 6 years of age are more prone to intussusception.

The present study also showed that hematochezia was an independent risk factor for the development of intussusception in children with HSP (OR = 5.355). This may be related to disease pathogenesis. Indeed, the current prevailing view is that submucosal bleeding and intestinal wall edema are the starting points of the mechanism underlying the development of HSP with GI involvement and concomitant intussusception in children[14]. Vasculitis involving capillaries and arterioles in the GI

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| Erythrocyte sedimentation rate, $n$ (%) | 0.388 |
|----------------------------------------|-------|
| $\leq 15$ mm/h                         | 50 (83.3) |
| $> 15$ mm/h                           | 10 (16.7) |
| D-dimer level, $n$ (%)                 | $< 0.001$ |
| $< 0.001$                              | 7 (11.7) |
| $\geq 1$ mg/L                         | 53 (88.3) |
| $< 1$ mg/L                            | 70 (70.0) |
| $\geq 1$ mg/L                         | 30 (30.0) |

GI: Gastrointestinal.
Table 2 Univariate and multivariate logistic regression analyses of risk factors for intussusception in children with Henoch-Schönlein purpura

| Risk Factor                  | Univariate          | Multivariate         |
|------------------------------|---------------------|----------------------|
|                              | OR                   | 95% CI               | P value | OR               | 95% CI          | P value |
| Age at onset                 | 0.121                | 0.052-0.284          | < 0.001 | 0.202            | 0.065-0.632     | 0.006   |
| First episode                | 4.750                | 1.347-16.748         | 0.015   | 6.705            | 0.840-53.537    | 0.073   |
| Duration of disease          | 0.195                | 0.043-0.887          | 0.034   | 0.208            | 0.018-2.382     | 0.207   |
| Glucocorticoid therapy within 72 h | 0.149                | 0.073-0.304          | < 0.001 | 0.342            | 0.127-0.920     | 0.034   |
| Vomiting                     | 5.021                | 2.518-10.012         | < 0.001 | 2.138            | 0.795-5.749     | 0.132   |
| Hematochezia                 | 7.508                | 3.511-16.056         | < 0.001 | 5.355            | 1.809-15.852    | 0.002   |
| White blood cell count       | 2.270                | 1.172-4.395          | 0.015   | 1.217            | 0.440-3.363     | 0.705   |
| D-dimer level                | 17.667               | 7.206-43.313         | < 0.001 | 7.193            | 2.507-20.640    | < 0.001 |

OR: Odds ratio; CI: Confidence interval.

Figure 1 Image of the small intestine of a 6-year-old girl who had intussusception and intestinal necrosis. A and B: A 6-year-old girl presented with a 12-h history of abdominal pain, vomiting, and purpura. She was diagnosed with Henoch-Schönlein purpura and intussusception. During the operation, the head of intussusception was found in the jejunum 50 cm away from the torus ligament, and the tail was found in the small intestine 30 cm away from the torus ligament. After reduction, the intestinal tubes were found to be black and purple in color. Enterectomy and anastomosis were performed, and the length of the diseased intestinal tubes was about 30 cm.

tract causes segmental bleeding from the subserosa and mucosa. Meanwhile, extensive edema of the intestinal mucosa, enlarged mesenteric lymph nodes, GI dysfunction, irregular peristalsis, and GI tract spasm lead to intussusception[15]. It is admitted that GI bleeding is more common in pediatric cases of HSP with GI involvement and intestinal perforation[16]. Furthermore, GI bleeding is a key factor in prolonged hospital stay in children with HSP[17]. In pediatric HSP patients with GI involvement, hematochezia and abdominal pain should be assessed as possible reasons for acute surgical abdomen. However, HSP with GI involvement often lacks specific clinical manifestations. Therefore, few children in the above intussusception group exhibited differential signs requiring surgical treatment, including abdominal mass, rebound tenderness, and hypoactive bowel sounds. It is necessary to perform abdominal color Doppler ultrasound imaging to screen for surgical complications.

D-dimer is a specific degradation product resulting from the hydrolysis of fibrinogen into fibrin monomer by thrombin, followed by crosslinking with activated factor XII and plasmin hydrolysis[18]. D-dimer plays an important role in the human
HSP is primarily caused by sub-endothelial deposition of immune complexes, leading to vascular endothelial cell damage, followed by coagulation system activation and microthrombosis. This induces the fibrinolytic system and increases D-dimer levels. Recent studies have shown that serum D-dimer levels are significantly higher in children with HSP compared with healthy controls. It was also shown that D-dimer levels reflect the severity of HSP, especially the extent of GI damage. Furthermore, D-dimer levels are more closely related to HSP symptoms in children than other general inflammatory parameters such as white blood cell count and C-reactive protein level. The present study revealed high D-dimer levels as an independent risk factor for intussusception in children with HSP, which is consistent with the above reports (OR = 7.193). Whether D-dimer can be used as a prognostic marker in children with HSP requires further investigation in large-scale clinical trials.

Different from classical intussusception in the ileocecum, the most common type of intussusception in HSP was ileal intussusception (51%), followed by ileocolic intussusception (39%), and other types were rare. In the present study, of 48 children with intussusception treated by operation, small intussusception was found in 29 (60.4%) cases, which was consistent with the reports in the literature. It was considered that the intestinal involvement of abdominal type HSP was the most common. This is because the small intestine is the main part of digestion and absorption, the contact area with chyme or related irritants is the widest, and the distribution of capillaries is abundant. The submucosa of the small intestine not only forms a capillary network between the intestinal glands, but also forms a capillary network close to the epithelium in the intestinal villi. The submucosa of the stomach and large intestine only forms a capillary network between the glands, so the small intestine is more involved than the colon.

Intussusception is the most common acute abdomen of HSP, and its surgical treatment includes air enema, water enema, and surgical treatment. Because the secondary changes such as edema and bleeding of the intestinal wall in children with HSP are serious, the success rate of air enema is relatively low. In the present study, the success rate of air enema was only 13.3% in 60 patient and 48 cases underwent surgical treatment. And there were intestinal necrosis in 18 cases, intestinal perforation in 2, and enterectomy in 16. Because HSP is a self-limited disease, it is feasible to diagnose early and avoid unnecessary surgery. However, in the process of conservative treatment, experienced surgical teams are needed to closely observe the changes of patients' conditions. There was a view that for older children or adults, surgery should be carried out as soon as possible to avoid delay in treatment. For patients with intussusception, the most serious complication of conservative treatment is intestinal perforation. Once there are signs of intestinal ischemic necrosis and intestinal perforation, surgical treatment is needed. For patients with short intussusception and good intestinal condition, simple manual reduction can be performed. If intestinal viability is suspected during surgery, enterostomy is recommended to avoid iatrogenic intestinal perforation. Many studies have shown that glucocorticoid therapy is beneficial for shortening the duration of abdominal pain, and reducing the risk of development of intussusceptio.
ception and the need for surgical intervention [25]. However, the value of glucocorticoids in the treatment of HSP remains controversial [26]. Studies have suggested that glucocorticoids increase the risk of GI ulcers, bleeding, and even perforation [16]. As shown above, no glucocorticoid therapy within 72 h of emergence of GI symptoms was an independent risk factor for intussusception in children with HSP and GI involvement (OR = 0.342). The regression coefficient was negative, supporting the viewpoint that early application of glucocorticoid therapy in HSP with GI involvement is beneficial to intussusception prevention. However, the clinical dosage and duration of glucocorticoids in HSP are not standardized. Further clinical studies are required to standardize this treatment and avoid the associated adverse effects. To the best of our knowledge, surgical resection is always the first choice for the treatment of adult intussusception to avoid the accident of intestinal perforation [27]. However, no unified clinical treatment standard for intussusception is currently available in children, and there is no clinical or imaging evidence to suspect that intussusception in children with perforation and peritonitis could be treated by enema reduction. However, it is reported that 58% of intussusception cases in children with HSP occurred in the small intestine [26], which may lead to a low success rate of enema reduction, and make most of them still need surgical treatment.

This study had several limitations. First, it was a retrospective study, with inherent shortcomings. In addition, the sample size was very limited, and all patients were from the same institution. Furthermore, multiple potential risk factors were not investigated in detail, including the nature of stool blood (e.g., bloody, black, and tarry, or only positive for occult blood) and the exact glucocorticoid dosage. Therefore, large multicenter studies investigating the associations of the above factors with abdominal intussusception in children with HSP in greater depth are warranted.

CONCLUSION

In summary, age at onset below 6 years, not receiving glucocorticoid therapy within 72 h of onset of GI symptoms, hematochezia, and increased D-dimer levels are independent risk factors for intussusception in children with HSP with GI involvement. Caution is needed in children suffering from HSP with GI involvement and showing at least one of the abovementioned factors, to avoid further disease aggravation and intussusception.

ARTICLE HIGHLIGHTS

Research background
The incidence rate of intussusception in Henoch-Schönlein purpura (HSP) is about 5%. It is the most common surgical acute abdomen in children with HSP. However, few reports have assessed the etiology of intussusception in children with HSP due to low clinical incidence. In particular, the risk factors for intussusception in children with HSP are largely unknown.

Research motivation
The aim of this study was to identify risk factors for the development of intussusception in children with HSP and gastrointestinal (GI) involvement.

Research objectives
The aim of this study was to identify risk factors for the development of intussusception in children with HSP and GI involvement.

Research methods
Sixty children with HSP and intussusception who were hospitalized at Beijing Children’s Hospital Affiliated to Capital Medical University from January 2006 to December 2018 were selected. One hundred cases of abdominal HSP without intussusception at Beijing Children’s Hospital during the same period were randomly selected as a control group. The general clinical data of all HSP patients were investigated, including gender, age of onset, onset time, clinical symptoms and signs, laboratory examination, imaging manifestations, treatment measures, etc. Univariate and multiple logistic regression analyses were performed to identify possible risk factors.
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Research results
The 60 children in the intussusception group included 27 girls (45%) and 33 boys (55%), while 100 children in the non-intussusception group included 62 girls (62%) and 38 boys (38%). The median age was 6 years and 5 mo. Univariate and multivariate regression analyses showed that age of onset, failure to receive glucocorticoid treatment within 72 h after GI symptoms, hematochezia, and D-dimer levels were independent risk factors for intussusception in children with HSP (P < 0.05).

Research conclusions
Age at onset below 6 years, not receiving glucocorticoid therapy within 72 h of onset of GI symptoms, hematochezia, and increased D-dimer levels are independent risk factors for intussusception in children with HSP with GI involvement. Caution is needed in children suffering from HSP with GI involvement and showing at least one of the abovementioned factors, to avoid further disease aggravation and intussusception.

Research perspectives
In view of the above factors, it is necessary to conduct a large sample multicenter study.

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