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Original Article

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Nationwide Population-Based Epidemiologic Study on Childhood Intussusception in South Korea: Emphasis on Treatment and Outcomes

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: This was a nationwide population-based study conducted to investigate the epidemiology, treatment, disease outcomes, and associated factors of childhood intussusception in South Korea.
Methods: Data from the Korean National Health Insurance Service database on all patients <18 years old diagnosed with intussusception from 2007 to 2017 were analyzed.
Results: A total of 34,688 cases were identified among 30,444 patients. The overall incidence was 28.3/100,000 person-years with a male predominance. Most cases (83.1%) occurred in children <3 years old, with an annual incidence of 195.2, 200.1, and 118.6 cases per 100,000 children in their first, second, and third year of life, respectively. The median age at the first occurrence was 18.7 months, and it was higher in boys than in girls. The post-discharge recurrence rate was 10.6% (3,226/30,444) and the in-hospital recurrence rate was 6.1% (1,842/30,444). The total recurrence rate (post-discharge recurrence and/or in-hospital recurrence) was 15.0% (4,580/30,444). Enema reduction was successful in 90.0% of cases. Enema reduction was more successful in girls than in boys. A total of 3,296 (10.8%) patients underwent 3,481 surgeries, including 735 (21.1%) laparoscopic surgeries. Post-discharge recurrence and surgery were significantly affected by age, sex, and hospital type. Mortality was noted in nine cases (0.03%).
Conclusion: Our study provides accurate epidemiologic data on the treatment and outcomes of intussusception through complete enumeration during an 11-year-period.

Keywords: Intussusception; Epidemiology; Treatment; Outcome; Child

INTRODUCTION

Intussusception is the most common cause of acute bowel obstruction in infants and young children [1]. Intussusception is a medical emergency because it may lead to bowel necrosis and perforation due to reduced arterial blood supply and cause peritonitis and even death, if not promptly diagnosed and treated [2,3]. Ileocolic intussusception, the most common type in children, requires reduction with ultrasound-guided or fluoroscopic pneumatic or hydrostatic enema, and is successful in most cases [4]. Small-bowel intussusception, which

is uncommon in children, can usually be safely monitored and often spontaneously reduces [4]. Regardless of the type of intussusception, surgical intervention is indicated when enema reduction or close observation is unsuccessful [3].

To date, many studies have examined the epidemiology, treatment, and clinical outcomes of childhood intussusception mainly based on hospital data, whereas nationwide population-based studies are limited. In recent years, some nationwide studies from Taiwan and Italy were published [5,6]; however, they included only inpatients.

The aim of this nationwide population-based study was to investigate the epidemiology, treatment, clinical outcomes, and factors associated with the disease outcomes of childhood intussusception in South Korea through complete enumeration.

MATERIALS AND METHODS

Data extraction

As the Korean government has been operating one mandatory nationwide health insurance system, the Korea National Health Insurance Service (NHIS), that covers the whole nation since 2000, all health-care utilization information is registered in a comprehensive Health Insurance Review and Assessment Service (HIRA) database. We used the HIRA database based on the Korea NHIS system. This database uses the International Classification of Disease, 10th revision (ICD-10) codes. The following data were extracted from the medical claim records: sex, age, date of hospital visit, admission and discharge dates, primary diagnosis and comorbidity code of ICD-10, hospitalization or outpatient care or emergency department visit, hospitalization length, and therapeutic interventions. Data on clinical symptoms and signs, results of medical investigations, exact time of starting the reduction procedure, specific pathology, and detailed surgical records were not available.

All Korean children <18 years old, treated for intussusception from January 1, 2007, to December 31, 2017, were enrolled. A true incidence case was defined as a visit with both the intussusception diagnosis code (K561) and a procedure code for reduction or a surgical intervention code. Procedure codes included M6781 (barium reduction of intussusception–success) and HA031 or HA032 (barium enema contrast study). Surgical codes included M6782 (barium reduction of intussusception–failure); Q2440 (diagnostic exploratory laparotomy); Q2650 (resection of the small intestine); Q2671, Q2673 (hemicolectomy, segmental resection of the colon); Q2680 (intestinal anastomosis); Q2691, Q2692, Q2693 (operation for intestinal obstruction including resection of the intestine, entero-enterostomy, adhesiolysis); Q2792, Q2793, Q2794 (enterostomy); or Q2810 (adhesiolysis). Laparoscopic surgery was identified by a laparoscopic surgical equipment code (N0031001).

Therefore, patients without a fluoroscopic pneumatic/barium enema or surgical intervention for reduction on claim data were excluded although the K561 code was applied. Post-discharge recurrence was defined as revisiting a hospital or re-admission with both the K561 code and a radiologic/surgical intervention code for reduction. Conversely, in-hospital recurrence was defined as a relapse in one admission or one hospital visiting period. The episodes of in-hospital recurrence were calculated using repeated procedure codes for enema in one admission or one hospital visiting period. The occurrence day of intussusception was defined as the first day of visiting a hospital or hospitalization. In cases of children who

underwent surgery for intussusception, we identified all accompanying diagnosis codes to presume possible pathologic leading points.

Data on mortality due to intussusception in children aged <18 years in South Korea were derived from Statistics Korea (Korean National Statistical Office; https://mdis.kostat.go.kr).

Statistical analysis

The first episode of intussusception was used to calculate the disease incidence. The incidence rate was calculated by dividing the number of new cases by the corresponding population size, as published by Statistics Korea. The average age- and sex-specific incidence rate was calculated by dividing the number of new cases in each age and sex group by the age- and sex-specific population size of those aged <18 years from 2007 to 2017. The population data for South Korea were derived from the website of Statistics Korea (http://kostat.go.kr/portal/eng/index.action).

The annual intussusception incidence rates are presented as incidence per 100,000 children and calculated by dividing annual new cases by each mid-year population of those aged <18 years. The incidence rate ratio (IRR) and 95% confidence interval (CI) were calculated using Poisson regression. Quantitative variables were analyzed using independent t test for parametric variables and the Mann-Whitney U-test for non-parametric variables. Categorical variables were compared using the chi-square test.

To assess associated factors for post-discharge recurrence and surgery, multivariate logistic regression analysis was performed. A p-value of <0.05 was considered significant. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Ethical statement

The Institutional Review Board of Seoul National University Bundang Hospital approved this study (approval No. X-1803-459-904). All methods were performed in accordance with the relevant guidelines and regulations approved by the Institutional Review Board of Seoul National University Bundang Hospital, Korea. The requirement for informed consent was waived because all analysis used anonymous data.

RESULTS

Incidence rate of childhood intussusception in South Korea

A total of 34,688 intussusception episodes in 30,444 children aged 0–17.9 years were recorded (**Table 1**). The overall incidence of intussusception was 28.3/10^5 person-years with a male predominance (male-to-female IRR 1.64, 95% CI 1.61–1.68, p<0.0001). The annual incidence decreased except in 2010 from 30.2/10^5 person-years in 2007 to 23.9/10^5 person-years in 2017 with a steady decline in the mid-year population (2007, 109 million; 2017, 86 million) (**Table 2**, **Fig. 1**). The age-specific incidence peaked in 1-year-old children, reaching as high as 200.1/10^5 person-years; the incidence was 195.2/10^5 person-years in infants <1 year old and 118.6/10^5 person-years in 2-year-old children (**Table 3**, **Fig. 2**). The age-specific incidence rapidly decreased with age. The cumulative percentage of intussusception was 30.5% in infants <1 year old, 63.4% in children <2 years old, 83.1% in children <3 years old, and 95.6% in children <5 years old (**Table 3**, **Fig. 2**).

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Table 1. Characteristics of pediatric intussusception cases during the overall study duration (2007–2017) in South Korea

Variable	No. of patients	Incidence (/10^5 person-yr)	IRR (95% CI)	Age (mo)
Total patients	30,444 (100.0)	28.3		18.7 (10.6–30.1)*
Boys	19,530 (64.2)	34.8	1.64 (1.61–1.68)	19.7 (11.2–31.4)*
Girls	10,914 (35.8)	21.2	Reference	16.9 (9.8–27.7)*
Only one admission or hospital visit	27,218 (89.4)	25.3		19.0 (10.8–30.5)
Only enema procedure	24,577 (80.7)	22.8		19.1 (11.0–30.1)
Surgery after enema failure	666 (2.2)	0.6		16.3 (8.5–29.8)
Primary surgery	1,975 (6.5)	1.8		17.5 (8.9–38.0)
Post-discharge recurrence	3,226 (10.6)	3.0		21.1 (11.8–33.2)
Only enema reduction	2,572 (8.4)	2.4		21.4 (12.2–33.2)
Surgery after enema failure	552 (1.8)	0.5		23.9 (12.6–40.2)
Primary surgery without enema	102 (0.3)	0.1		15.7 (8.0–32.5)
Number of post-discharge recurrences	3,226 (100.0)	3.0		
1	2,562 (79.4)	2.4		
2	466 (14.4)	0.4		
3	129 (4.0)	0.1		
4	36 (1.1)	0.03		
≥5	33 (1.0)	0.03		

Values are presented as number (%) or median (interquartile range). The incidence was calculated by dividing the number of new cases by the corresponding population size as published by Statistics Korea (Korean National Statistical Office).
IRR: incidence rate ratio, CI: confidence interval.
The IRR and 95% CI were calculated using Poisson regression.
*Children's age at the first intussusception occurrence.

Table 2. Annual incidence of pediatric intussusception in South Korea

Year	New cases of intussusception			Incidence (per 10^5 person-years)						M/F incidence ratio
	Boys	Girls	Total	Boys	Girls	Total	IRR	IRR 95% CI	*p*-value	
2007	2,140	1,156	3,296	37.4	22.4	30.2	Reference			1.67
2008	1,887	1,036	2,923	33.5	20.3	27.2	0.90	0.86–0.95	<0.0001	1.65
2009	1,714	987	2,701	31.1	19.7	25.7	0.85	0.81–0.89	<0.0001	1.58
2010	2,212	1,189	3,401	41.2	24.3	33.1	1.10	1.04–1.15	0.0002	1.70
2011	1,668	912	2,580	31.9	19.0	25.7	0.85	0.81–0.90	<0.0001	1.67
2012	1,785	979	2,764	35.0	20.9	28.2	0.93	0.89–0.98	0.0076	1.68
2013	1,891	1,110	3,001	38.1	24.2	31.4	1.04	0.99–1.09	0.1265	1.58
2014	1,567	931	2,498	32.5	20.8	26.9	0.89	0.84–0.94	<0.0001	1.56
2015	1,586	879	2,465	33.8	20.1	27.2	0.90	0.85–0.95	<0.0001	1.68
2016	1,747	1,015	2,762	38.2	23.8	31.3	1.03	0.98–1.09	0.2011	1.61
2017	1,333	720	2,053	30.0	17.3	23.9	0.79	0.75–0.83	<0.0001	1.73
Total	19,530	10,914	30,444	34.8	21.2	28.3				1.64

The annual incidence of pediatric intussusception was calculated by dividing annual new cases by each mid-year population aged <18 years.
M: male, F: female, IRR: incidence rate ratio, CI: confidence interval.
IRR, 95% CI, and *p*-values were calculated using Poisson regression.

The median age at the first intussusception occurrence was 18.7 months, and was higher for boys than for girls (19.7 months vs. 16.9 months, $p<0.001$).

Post-discharge recurrence and in-hospital recurrence of childhood intussusception

Of 30,444 children, 27,218 (89.4%) reported only one occurrence, whereas 3,226 (10.6%) reported one or more post-discharge recurrences (**Table 1**). There were 7,470 occurrences of intussusception with 4,244 episodes of post-discharge recurrences in 3,226 children. Most children with post-discharge recurrences (93.9%) had one (79.4%) or two (14.4%) post-discharge recurrence episodes (**Table 1**). The median time to the first post-discharge recurrence was 72 days (minimum 0 days, maximum 8.2 years). Conversely, 1,842 children (6.1% of the total 30,444 children) had several in-hospital recurrences within one admission or one hospital visiting period (**Table 4**). Of 27,218 children with only one intussusception admission or one hospital visit, 1,354 (5.0% of 27,218) had a mean of two in-hospital

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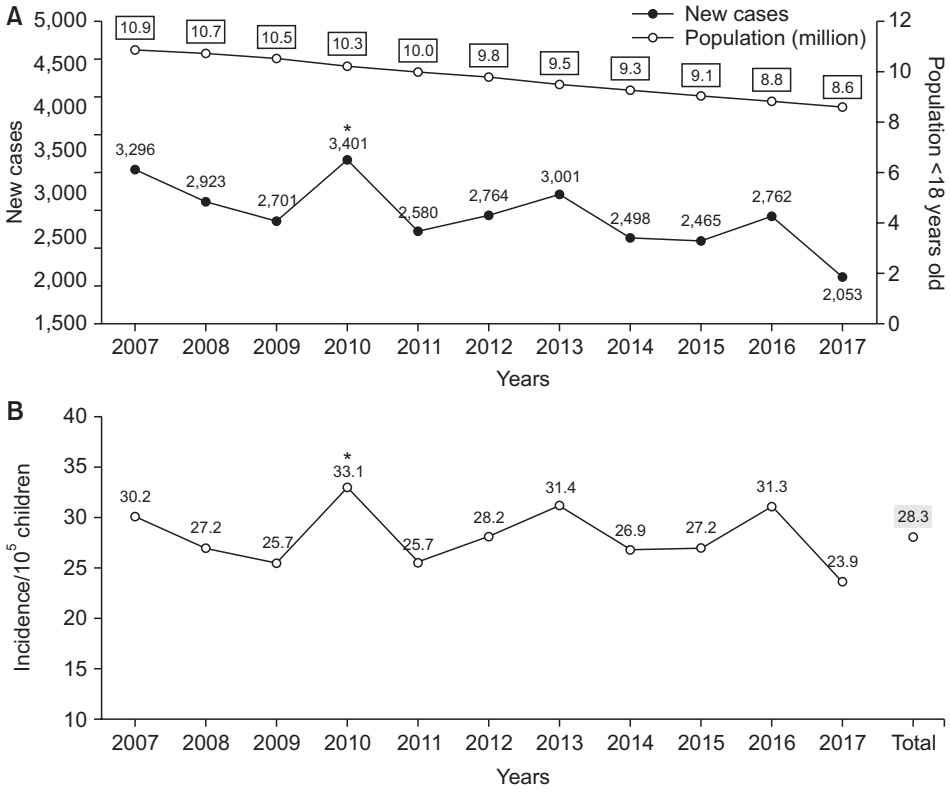

Fig. 1. Annual incidence of intussusception in patients <18 years old between 2007 and 2017 in South Korea. (A) Annual new cases of intussusception and annual mid-year population. (B) The annual incidence, except in 2010, generally decreased from 30.2/10^5 person-years in 2007 to 23.9/10^5 person-years in 2017 based on the incidence in 2007 as the mid-year population continuously decreased from 109 million in 2007 to 86 million in 2017. The incidence in 2013 and 2016 were not statistically significantly different. *The incidence in 2010 was significantly higher than that in 2007. The overall intussusception incidence was 28.3/10^5 person-years.

recurrences (maximum of five) in each medical statement (**Table 4**). Of 3,226 patients with post-discharge recurrence (one or more re-admissions/revisits), 565 admissions/hospital visits of 488 (15.1% of 3,226) children had a mean of two in-hospital recurrences (maximum of four) in each medical statement. The total recurrence rate (children with post-discharge recurrence and/or in-hospital recurrence) was 15.0% (4,580 [2,738+1,842]/30,444) (**Table 4**). Patients with post-discharge recurrence had more in-hospital recurrences within one admission/hospital visiting period than those with only one admission/hospital visit for intussusception (15.1% vs. 5.0%, p<0.001) (**Table 4**).

Treatment interventions for childhood intussusception

Of 34,688 cases, 31,207 (90.0%) were successfully resolved with non-surgical treatment such as pneumatic/barium enema procedures. A total of 3,481 (10.0%) cases required surgical interventions (primary surgery without enema reduction or surgery after enema reduction failure) (**Table 5**). Surgery after enema reduction failure and emergency surgery without enema reduction were performed in 2.4% and 7.6% of cases, respectively (**Table 5**). Non-surgical enema reduction was more successful in girls than in boys (91.1% vs. 89.4%, p<0.001) (**Table 5**). Patients who needed surgical intervention were younger than those whose conditions were resolved with non-surgical enema reduction (17.4 months vs. 19.6 months, p<0.001) (**Table 5**). A higher success rate with non-surgical intervention was observed in children <3 years old than in those >3 years old (91.0% vs. 86.7%, p<0.001).

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Table 3. Age- and sex-specific incidence of childhood intussusception in South Korea

Age (yr)	New cases of intussusception					Incidence (per 10^5 person-years)					*p*-value	M/F incidence ratio
	Boys	Girls	Total	Fraction (%)	Accumulation (%)	Boys	Girls	Total	IRR	IRR 95% CI		
0	5,519	3,751	9,270	30.45	30.45	226.0	162.6	195.2	35.18	34.01–36.40	<0.0001	1.39
1	6,338	3,697	10,035	32.96	63.41	245.7	151.8	200.1	36.07	34.88–37.30	<0.0001	1.62
2	4,024	1,967	5,991	19.68	83.09	154.7	80.2	118.6	21.37	20.59–22.18	<0.0001	1.93
3	1,826	838	2,664	8.75	91.84	69.5	33.9	52.2				2.05
4	827	306	1,133	3.72	95.56	31.1	12.3	21.9				2.53
5	391	143	534	1.75	97.32	14.5	5.7	10.2				2.55
6	169	62	231	0.76	98.08	6.1	2.4	4.3				2.54
7	111	47	158	0.52	98.59	3.9	1.8	2.9				2.19
8	58	24	82	0.27	98.86	2.0	0.9	1.5	Reference (≥3 yr)			2.24
9	64	12	76	0.25	99.11	2.1	0.4	1.3				4.92
10	38	12	50	0.16	99.28	1.2	0.4	0.8				2.91
11	38	14	52	0.17	99.45	1.2	0.5	0.8				2.49
12	29	7	36	0.12	99.57	0.8	0.2	0.6				3.77
13	35	8	43	0.14	99.71	1.0	0.3	0.6				3.96
14	20	6	26	0.09	99.79	0.5	0.2	0.4				3.00
15	16	9	25	0.08	99.88	0.4	0.3	0.3				1.60
16	18	7	25	0.08	99.96	0.5	0.2	0.3				2.30
17	9	4	13	0.04	100.00	0.2	0.1	0.2				2.01
Total	19,530	10,914	30,444	100.00		34.8	21.2	28.3				1.64

The age- and sex-specific incidence was calculated by dividing the number of new cases in each age and sex group by the age- and sex-specific population size of children aged <18 years from 2007 through 2017.
M: male, F: female, IRR: incidence rate ratio, CI: confidence interval.
IRR, 95% CI, and *p*-values were calculated using Poisson regression.

Surgical treatments and accompanying diagnosis codes in surgical cases of intussusception

Of 30,444 patients, 3,295 (10.8%) underwent 3,481 surgeries for intussusception. The characteristics of surgeries for intussusception are presented in **Table 6**. As the annual number of new cases of intussusception decreased, the annual number of surgeries and laparotomies also decreased. However, the number of laparoscopic surgeries continuously increased (**Fig. 3**).

Accompanying diagnosis codes in surgical cases of intussusception were identified to presume possible pathologic leading points (**Table 7**). Of 3,481 medical claim data of surgeries, 728 (20.9%) surgical cases had 786 accompanying diagnosis codes, with the intussusception diagnosis code in 713/3,295 (21.6%) children. The most common comorbidity was appendix problems such as inflamed appendix and appendicitis (46.1%); the second was lymphadenitis or lymph node disorders (13.0%); and the third was Meckel's diverticulum (8.9%). When surgical cases were divided into children <6 years old and children ≥6 years old, the most common comorbidity in children ≥6 years old was benign neoplasm of the gastrointestinal tract including polyps or Peutz-Jeghers syndrome (22.6%). The second most common comorbidity was appendix problems (20.5%), followed by lymphoma (17.9%) and Meckel's diverticulum (11.3%) (**Table 7**).

Mortality related to childhood intussusception

From 2007 to 2017, nine mortality cases (about 0.03% of 30,444 patients) were related to intussusception, including one male infant in 2007, one male infant in 2009, two female infants and one 3-year-old girl in 2010, one female infant and one 4-year-old girl in 2012, one 10-year-old boy in 2014, and one male infant in 2016.

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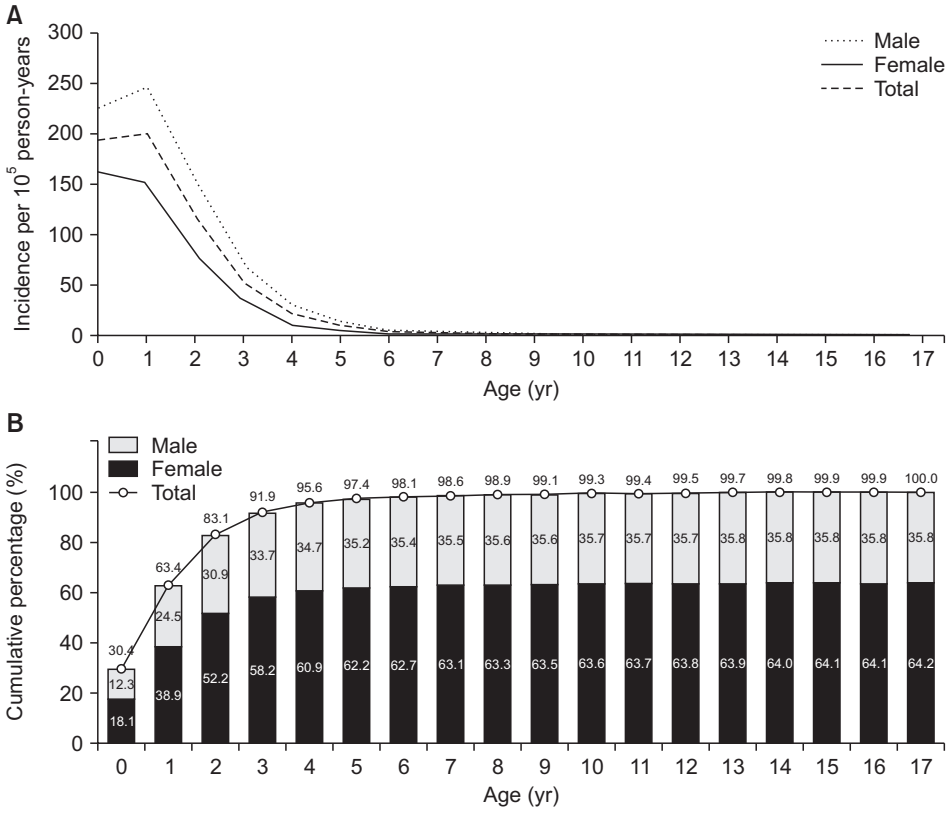

Fig. 2. Age- and sex- specific incidence of intussusception in patients <18 years of age between 2007 and 2017 in South Korea. (A) Age- and sex- specific incidence at every 1 year in patients younger than 18 years. The incidence is presented per 10^5 person-years. (B) Cumulative percentage of age- and sex-specific incidence.

Table 4. In-hospital recurrence and post-discharge recurrence of pediatric intussusception

Accompanied	Only one admission or one hospital visit	Revisiting a hospital or re-admission (post-discharge recurrence)	Total patients
No in-hospital recurrence	25,864 (95.0)	2,738 (84.9)	28,602 (93.9)
In-hospital recurrence	1,354 (5.0)	488 (15.1)	1,842 (6.1)
	27,218 (100.0)	3,226 (100.0)	30,444 (100.0)

Values are presented as number (%).
Post-discharge recurrence was defined as revisiting a hospital or re-admission for intussusception. In-hospital recurrence was defined as a relapse in one admission or one hospital visiting period. The post-discharge recurrence rate was 10.6% (3,226/30,444) and the in-hospital recurrence rate was 6.1% (1,842/30,444). The total recurrence rate (children with post-discharge recurrence and/or in-hospital recurrence) was 15.0% (4,580 [2,738+1,842]/30,444). Patients with post-discharge recurrence had a higher incidence of in-hospital recurrence than children with only one admission/hospital visit for intussusception (15.1% vs. 5.0%, $p<0.001$).
The p-value was calculated using the chi-square test.

Table 5. Non-surgical reduction and surgical treatment among the entire childhood intussusception cases

Variable	Non-surgical enema reduction (air or barium enema)	Surgery			Total intussusception cases	p-value
		Total surgical cases	Surgery after enema failure	Primary surgery		
Total	31,207 (90.0)	3,481 (10.0)	835 (2.4)	2,646 (7.6)	34,688 (100.0)	<0.001*
Boys	20,104 (89.4)	2,396 (10.6)	566 (2.5)	1,830 (8.1)	22,500 (100.0)	<0.001†
Girls	11,103 (91.1)	1,085 (8.9)	269 (2.2)	816 (6.7)	12,188 (100.0)	
Age (mo)	19.6 (11.3–30.8)	17.4 (8.6–35.0)	18.2 (9–31.8)	17.2 (8.6–36.5)	19.4 (10.9–31.1)	<0.001‡

Values are presented as number (%) or median (interquartile range).
*The p-value between non-surgical enema reduction treatment and surgical treatment was calculated using the chi-square test. †The difference of non-surgical treatment and surgical treatment between boys and girls was calculated using the chi-square test. ‡The age difference (19.6 vs. 17.4 months) between the non-surgical enema reduction group and the surgical treatment group was calculated using the Mann-Whitney U-test.

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Table 6. Characteristics of surgical interventions for childhood intussusception

Variable	Value	*p*-value
Sex		
Boys	2,268 (68.8)	<0.001
Girls	1,027 (31.2)	
Age (mo)		
Total	17.4 (8.6–35.2)	
Boys	19.0 (9.1–37.4)	<0.001*
Girls	14.5 (7.8–29.3)	
Primary surgery vs. surgery after enema failure	2,646 (75.8)	<0.001
	835 (23.9)	
Laparotomy vs. laparoscopy	2,746 (78.9)	<0.001
	735 (21.1)	
Bowel resection vs. non-bowel resection	648 (18.6)	<0.001
	2,833 (81.4)	
Seasonal distribution		<0.001
Spring	918 (26.4)	
Summer	948 (27.2)	
Autumn	849 (24.4)	
Winter	766 (22.0)	
Type of hospital		
Tertiary hospital	1,829 (52.5)	<0.001
General hospital	1,616 (46.4)	
Hospital	36 (1.0)	
Length of hospitalization (d)	6.0 (4–8)	
Number of surgeries		<0.001
1	3,124 (94.8)	
2	161 (4.9)	
≥3	10 (0.3)	

Values are presented as number (%) or median (Interquartile range).
A total of 3,295 (10.8%) patients among 30,444 pediatric intussusception patients had 3,481 surgeries.
*The *p*-value of age between boys and girls was calculated using the Mann-Whitney U-test. Other *p*-values were calculated using the chi-square test.

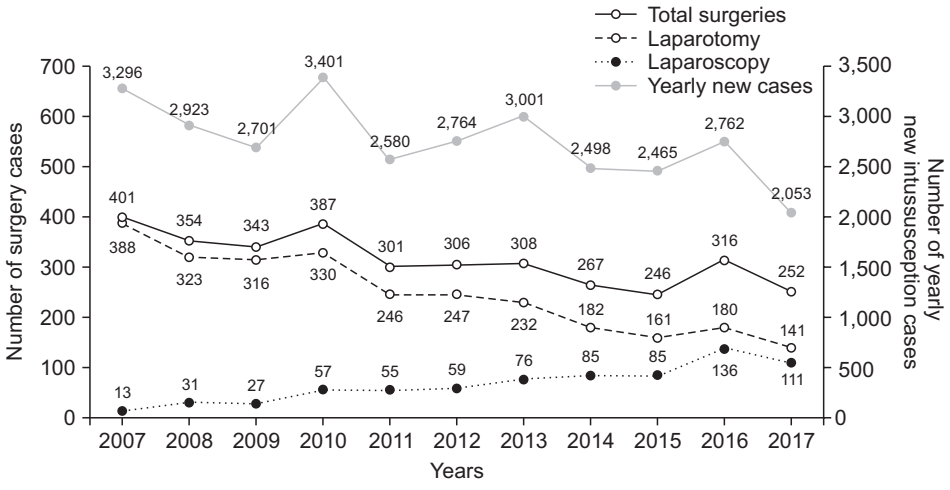

Fig. 3. Annual numbers of surgeries in children with intussusception between 2007 and 2017 in South Korea. As annual new cases of intussusception decreased, the annual surgery numbers and laparotomy numbers also decreased. However, the laparoscopic surgery numbers continuously increased.

Associated factors for occurrence, post-discharge recurrence, and surgery of childhood intussusception

Multiple logistic regression analysis was performed to identify factors associated with pediatric intussusception in the first occurrence and in total occurrences (**Table 8**). The

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Table 7. Accompanying diagnosis codes in surgical cases of pediatric intussusception

Accompanying diagnosis in surgical cases	Total number	Age (yr)	
		<6	6≤, <18
Appendicitis, inflamed appendix, appendix problems	362 (46.1)	322 (54.5)	40 (20.5)
Lymphadenitis, lymph node disorder	102 (13.0)	85 (14.4)	17 (8.7)
Meckel's diverticulum	70 (8.9)	48 (8.1)	22 (11.3)
Malrotation, congenital malformations including malformation of intestinal fixation, intestinal adhesions (bands) with obstruction	63 (8.0)	54 (9.1)	9 (4.6)
Lymphoma	47 (6.0)	12 (2.0)	35 (17.9)
Benign neoplasm of the GI tract, GI tract polyp, Peutz-Jeghers syndrome	67 (8.5)	23 (3.9)	44 (22.6)
Vascular disorder of intestine	20 (2.5)	12 (2.0)	8 (4.1)
Henöch-Schönlein purpura	18 (2.3)	10 (1.7)	8 (4.1)
Diverticular disease of the intestine	12 (1.5)	10 (1.7)	2 (1.0)
Malignant neoplasm of the GI tract	5 (0.6)	6 (1.0)	0 (0.0)
Duplication of the intestine	6 (0.8)	0 (0.0)	5 (2.6)
Hirschsprung disease	4 (0.5)	4 (0.7)	0 (0.0)
Benign neoplasm of intra-abdominal soft tissue (including peritoneum)	4 (0.5)	3 (0.5)	1 (0.5)
Leukemia	3 (0.4)	1 (0.2)	2 (1.0)
Kawasaki disease	2 (0.3)	1 (0.2)	1 (0.5)
Malignant neoplasm of intra-abdominal soft tissue	1 (0.1)	0 (0.0)	1 (0.5)
	786 (100.0)	591 (100.0)	195 (100.0)

Values are presented as number (%).
GI: gastrointestinal.
In a total of 30,444 pediatric intussusception patients, 3,295 children had 3,481 surgeries for intussusception. Among 3,481 medical claim data in the national Health Insurance Review and Assessment Service database, 728/3,481 (20.9%) surgical cases had 786 accompanying diagnosis codes with the intussusception diagnosis code in 713/3,295 (21.6%) children.

Table 8. Associated factors of pediatric intussusception in the first occurrence and in total occurrences

Variable	First occurrence						Total occurrences (first occurrence plus post-discharge recurrence)					
	No. of cases	%	OR	95% CI		*p*-value	No. of cases	%	OR	95% CI		*p*-value
Age (yr)												
0≤, <1	9,270	30.45	Reference				10,036	28.93	Reference			
1≤, <2	10,035	32.96	0.65	0.61	0.70	<0.0001	11,295	32.56	0.85	0.80	0.90	<0.0001
2≤, <3	5,991	19.68	0.62	0.57	0.67	<0.0001	7,037	20.29	0.95	0.89	1.02	0.1581
≥3	5,148	16.91	0.80	0.74	0.87	<0.0001	6,320	18.22	1.27	1.19	1.36	<0.0001
Sex												
Girls	10,914	35.85	Reference				12,188	35.14	Reference			
Boys	19,530	64.15	1.34	1.26	1.43	<0.0001	22,500	64.86	1.32	1.26	1.39	<0.0001
Season												
Spring (Mar to May)	7,413	24.35	Reference				8,401	24.22	Reference			
Summer (Jun to Aug)	8,782	28.85	0.92	0.85	0.99	0.0288	10,040	28.94	0.97	0.91	1.03	0.2908
Autumn (Sep to Nov)	8,093	26.58	0.90	0.83	0.98	0.0113	9,233	26.62	0.98	0.91	1.04	0.4464
Winter (Dec to Feb)	6,156	20.22	1.00	0.92	1.09	0.9640	7,014	20.22	1.03	0.96	1.10	0.4143
Type of hospital												
Hospital	274	0.90	1.01	0.74	1.37	0.9630	297	0.86	0.84	0.65	1.10	0.2074
General hospital	15,043	49.41	Reference				16,907	48.74	Reference			
Tertiary hospital	15,127	49.69	1.08	1.02	1.14	0.0119	17,484	50.40	1.16	1.11	1.22	<0.0001
Total cases	30,444	100.00					34,688	100.00				

OR: odds ratio, CI: confidence interval, Mar: March, Jun: June, Aug: August, Sep: September, Nov: November, Dec: December, Feb: February.
OR and CI were analyzed using a multiple logistic regression model.

odds ratio (OR) of the first intussusception occurrence decreased as the age at the initial onset increased; however, compared with the total number of intussusception occurrences in infants <1 year old, 1-year-old children had lower occurrences (OR 0.85) and children ≥3 years old had higher occurrences (OR 1.27). Boys showed higher OR than girls in both the first occurrence and in the total number of occurrences (OR 1.34 and 1.32, respectively). Incidences in summer and autumn were lower than incidences in spring at the initial onset (OR 0.92 and 0.90, respectively); however, seasonal variation was not significantly different

for the total number of occurrences. Visits to tertiary hospitals were more common than visits to general hospitals, for both initial episodes and the total number of occurrences (OR 1.08 and 1.16, respectively).

Multiple logistic regression analysis was performed to identify associated factors for post-discharge recurrences and surgeries of intussusception (**Table 9**). As patient age increased, post-discharge recurrences increased; however, compared with infants <1 year old, surgeries decreased in children <3 years old. For both post-discharge recurrences and surgeries, boys showed higher OR (1.30 and 1.23, respectively). Seasonal variation was not prominent for post-discharge recurrences; however, in cases of surgery, summer and autumn showed lower OR than spring (0.84 and 0.80, respectively). In both post-discharge recurrences and surgeries, tertiary hospitals showed higher OR than general hospitals (1.17 and 1.10, respectively). In cases of post-discharge recurrences, the risks for surgery increased compared with cases without post-discharge recurrence (OR 1.17).

Hospitalization and direct medical costs of childhood intussusception

According to hospitalization and the type of treatment of intussusception, the mean duration of hospitalization and direct medical costs were significantly different (1.2–7.3 days and 210.6–2,280.1 US dollars [USD], respectively; p<0.001) (**Table 10**). Direct medical costs were higher for children ≥3 years old than in those <3 years old (633.7 USD vs. 762.4 USD, p<0.001).

Table 9. Associated factors of post-discharge recurrence and risks of surgical treatment in pediatric intussusception

Variable	Total cases	Post-discharge recurrence						Surgery					
		Cases (n)	%	OR	95% CI		*p*-value	Cases (n)	%	OR	95% CI		*p*-value
Age (yr)													
0≤, <1	10,036	1,936	19.29	Reference				1,319	13.14	Reference			
1≤, <2	11,295	2,313	20.48	1.08	1.01	1.16	0.0199	841	7.45	0.52	0.48	0.57	<0.0001
2≤, <3	7,037	1,650	23.45	1.28	1.19	1.38	<0.0001	482	6.85	0.47	0.42	0.53	<0.0001
≥3	6,320	1,571	24.86	1.36	1.26	1.46	<0.0001	839	13.28	0.98	0.89	1.07	0.6009
Sex													
Girls	12,188	2,254	18.49	Reference				1,085	8.90	Reference			
Boys	22,500	5,216	23.18	1.30	1.23	1.37	<0.0001	2.396	10.65	1.23	1.14	1.33	<0.0001
Season													
Spring (Mar to May)	8,401	1,772	21.09	Reference				918	10.93	Reference			
Summer (Jun to Aug)	10,040	2,195	21.86	1.04	0.97	1.12	0.2741	947	9.43	0.84	0.76	0.92	0.0003
Autumn (Sep to Nov)	9,233	1,990	21.55	1.05	0.97	1.13	0.2127	849	9.20	0.80	0.73	0.89	<0.0001
Winter (Dec to Feb)	7,014	1,513	21.57	1.04	0.97	1.13	0.2806	767	10.94	0.98	0.88	1.08	0.6830
Specialization of clinic													
Hospital	297	45	15.15	0.68	0.49	0.94	0.0177	36	12.12	1.30	0.91	1.86	0.1435
General hospital	16,907	3,424	20.25	Reference				1,616	9.56	Reference			
Tertiary hospital	17,484	4,001	22.88	1.17	1.11	1.24	<0.0001	1,829	10.46	1.10	1.02	1.18	0.0113
Post-discharge recurrence													
No	27,218							2,641	9.70	Reference			
Yes	7,470							840	11.24	1.17	1.08	1.27	0.0002
Surgery													
No	31,207	6,630	21.25	Reference									
Yes	3,481	840	24.13	1.17	1.08	1.27	0.0002						
Total cases	34,688	7,470						3,481					

OR: odds ratio, CI: confidence interval, Mar: March, Jun: June, Aug: August, Sep: September, Nov: November, Dec: December, Feb: February.
OR and 95% CI were calculated using multiple logistic regression analysis.

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Table 10. Length of hospitalization and direct medical costs of childhood intussusception in South Korea

	Cases	%	No. of patients	Mean length of hospitalization (days)	Mean direct medical costs (KRW)	Mean direct medical costs (USD)
Total	34,688	100.0	30,444	3.4	744,552	657.2
Treatment type, admission						
Enema reduction and non-admission*	3,940	11.4	3,734	1.2	238,660	210.6
Enema reduction and admission	27,267	78.6	24,593	3.2	582,900	514.5
Surgical treatment and admission	3,481	10.0	3,295	7.3	2,583,382	2,280.1
ICU admission	33	0.1	33	9.8	5,338,540	4,711.9
Age (yr)						
<3	28,368	81.8	25,296	3.3	717,980	633.7
3≤, <18	6,320	18.2	5,686	3.6	863,822	762.4

KRW: Korean won, USD: US dollars, ICU: intensive care unit.
In the present study, direct medical costs did not include non-insurance medical expenses such as ultrasound cost. Therefore, the real average medical cost of intussusception may be higher than that reported in our study.
*Non-admission included outpatient clinic visits and emergency department stays.
1 USD=1,133 KRW (exchange rate on November 15, 2018).

DISCUSSION

This was a nationwide population-based study conducted to elucidate the epidemiology, treatment, disease outcomes, and factors associated with disease outcomes of childhood intussusception in South Korea through complete enumeration.

The overall childhood intussusception incidence from 2007 to 2017 in South Korea was 28.3/10^5 person-years, which is similar to that in Italy (21/10^5 children ≤15 years old) but higher than that in Germany (10.4/10^5 children <15 years old) and Canada (3.0–4.3/10^5 person-years in children <18 years old) [7,8]. Geographical and environmental variations in intussusception incidence are known to exist [9,10]. Furthermore, the incidence differed according to race/ethnicity even within the same country [11,12]. In our study, the mean incidence in infants <1 year old was 195.2/10^5 person-years. A literature review showed that the global mean incidence of intussusception was 74/10^5 (range 9/10^5–328/10^5) among infants <1 year old [10]. The mean incidence of intussusception among infants <1 year old was higher in Asia and Australia (185/10^5 in Japan, 108/10^5 in Hong Kong, 77/10^5 in Taiwan, 101/10^5 in Australia) than in Europe and North America (66/10^5 in Denmark, 60/10^5 in Germany, 56/10^5 in Switzerland, 39/10^5 in Italy, 24/10^5 in England, 35/10^5 in the United States, 34/10^5 in Canada) [5-8,10,11,13-19]. The incidence of intussusception in Korea is higher than that in other countries. There are still gaps in variant incidence rate by region with respect to disease etiology and mechanisms [9].

In the present study, boys showed a higher incidence rate than girls (IRR 1.64). Male predominance in intussusception incidence has been noted in previous studies, with male-to-female ratios ranging from 1.2 to 2.5 [5-7,11,13,20]. The median age at the first occurrence of intussusception was 18.7 months, similar to studies from other countries (17 months in the United States and Japan, and 21.1 months in Germany) [7,13,21]. In our study, boys had a higher median age than girls (19.7 months vs. 16.9 months). Similarly, a previous Taiwanese study showed that age was higher in boys than in girls (27.3 months vs. 24.9 months) [5].

In our study, 3,226/30,444 children (10.6%) had one or more post-discharge recurrences. In the 30,444 cases of first intussusception incidence, 27,475 (90.2%) successfully resolved after enema reduction. Further, after a successful enema reduction, 2,899/27,475 (10.6%) had post-discharge recurrence. A total of 1,842/30,444 (6.1%) had in-hospital recurrences

within one admission or one hospital visiting period. The total recurrence rate (children with post-discharge recurrence and/or in-hospital recurrence) was 15.0% (4,580/30,444). A meta-analysis showed that the overall recurrence rates and the recurrence rates within 48 h after enema reduction, except for cases requiring surgery, were 7.5–12.7% and 2.7–6.6%, respectively [22]. A systematic review and meta-analysis showed an overall recurrence rate of 8.8% for the admission group and 10.1% for the emergency department management group [23]. Another systematic review and meta-analysis showed that the overall recurrence rate was 6% for inpatients and 8% for outpatients; however, the pooled estimate of re-admission rate could not be obtained owing to infrequency and inconsistency due to the small number of patients in each study [24]. In a nationwide study based on an inpatient-only database, excluding emergency department or outpatient clinic data, in Taiwan, the overall re-admission rate for intussusception in children <15 years old was 7.9% [5]. This was lower than the post-discharge recurrence rate in the present study. The difference is likely related to the inclusion of not only inpatients but also emergency department and outpatient clinic patients, among children <18 years old, in our study. Although based on data from one institute, recently published long-term retrospective studies showed a somewhat higher recurrence rate than previous studies [25,26]. The recurrence rate including both early recurrence (within 48 hours) and late recurrence (after 48 hours) was 13.8% (68/491) between January 2007 and January 2019 in a tertiary hospital in South Korea [25]. The total recurrence rate including both short-term recurrence (≤7 days) and long-term recurrence (>7 days) was 16.8% (115/683) between January 2000 and May 2018 in a tertiary hospital in the United States [26]. The median time to the first post-discharge recurrence was 72 days (minimum 0 days, maximum 8.2 years) in the present study. A long-term follow-up study has shown that recurrence of intussusception can occur not only within a short period but also several years after an intussusception episode [27].

In our study, the success rate of enema reduction was approximately 90% in first occurrence cases. In a literature review, the success rate of enema reduction was 67–85%, except in Africa and Central and South America [7,10]. The success rate of enema reduction in the first event was 79% in the United States [28], 87.7% in Italy [6], and 92.8% in Japan [13].

In our study, 3,296/30,444 patients (10.8%) underwent 3,481 surgeries for intussusception. This was similar to the results in Italy (9.9%) and Japan (7.2%) [6,13], but relatively lower than the results in other countries. A review article revealed that surgery was performed in 19% (range, 10–68%) of intussusception cases [9]. In another literature review, the overall surgery rate was 33% globally, 16% in Asia, 20% in Europe, 29% in Oceania, and 28% in North America [10].

In the present study, bowel resection was performed in 648/3,481 (18.6%) surgical cases, consistent with a previous review (18%, range 9–54%) [9]. In our study, approximately 2% of 34,688 intussusception cases were treated with bowel resection, consistent with a previous literature review showing that surgical bowel resection was performed in 7% globally, 3% in Asia, 3% in Central and South America, 5% in Europe, 9% in Oceania, and 11% in North America [10]. A recent study in Japan showed that 7.2% of the total cases were treated with surgery and 29.7% of the surgical cases (2.1% of total cases) involved bowel resection [13].

In our study, 728/3,481 surgical cases (20.9%, 2.1% of all intussusception occurrences) had 786 accompanying comorbidity diagnosis codes with the intussusception diagnosis code in 713/3,295 (21.6%) children. Some of them might be potential pathologic leading points. A

previous review reported that structural lead points were observed in 3% of patients [9]. A study in Japan also showed that 3.1% of cases had a pathologic lead point [13]. In our study, the common comorbidity diagnoses were appendix problems (46.1%), lymphadenitis or lymph node disorders (13.0%), and Meckel's diverticulum (8.9%). Similarly, in Italy, inflamed appendix was the most common comorbidity [6]. In Europe, enlarged mesenteric lymph nodes were found in 19–50% of pediatric intussusception patients undergoing surgery or investigation by ultrasound [9]. In Japan, the most common pathologic leading point was Henöch-Schönlein purpura followed by Meckel's diverticulum [13]. When surgical cases were divided into children <6 years old and children ≥6 years old, the most common comorbidity in children ≥6 years old was benign neoplasm of the gastrointestinal tract including polyps or Peutz-Jeghers syndrome (22.6%). The second most common comorbidity was appendix problems (20.5%), followed by lymphoma (17.9%). A Taiwanese study comparing child and adulthood intussusception also showed that children aged between 10 and 20 years had a substantially higher incidence of coexisting neoplasms and malignancies than children <10 years of age [29]. Ileal lymphoma, in particular, should be considered in any children with intussusception who are older than 6 years [30-32].

Our study showed that the initial occurrence of intussusception in summer and autumn was lower than that in spring; however, there was no significant difference in the total number of occurrences. Our results are consistent with a review that showed no seasonal patterns [10]. The seasonality of intussusception occurrence is still controversial in that many studies reported no seasonal variations [1,10,12,17,33-36] but several others showed seasonality [5,18,37].

Our multiple logistic regression analysis revealed that increasing age, male sex, and tertiary hospitals were associated with post-discharge recurrence of intussusception. The higher OR in tertiary hospitals than in general hospitals may be explained by the fact that pediatric patients might visit tertiary hospitals when intussusception had recurred after discharge. It is reasonable that hospital type is considered an associated factor, not a causal factor, of post-discharge recurrence.

Our multiple logistic regression analysis also revealed that age, sex, seasonality, and hospital type were factors associated with surgery. The higher OR with surgeries in tertiary hospitals than those in general hospitals may be explained by the fact that children might often be transferred to tertiary hospitals when surgical treatment is required. The hospital type can be considered an associated factor, rather than a causal factor, of surgery for intussusception. Furthermore, in cases of post-discharge recurrence, the need for surgery increased compared with that in cases without post-discharge recurrence.

Mortality from intussusception is generally rare (0.03–0.07%), except in Africa [1,10,11,13]. In Italy, the mortality rate of pediatric intussusception was 0.04% [6]. In our study, there were nine mortality cases (four boys and five girls, <1 year old in six cases and ≥3 years old in three cases), showing a mortality rate of 0.03%.

Although recent nationwide studies were performed in Italy, Taiwan, and Japan, they did not cover outpatient settings or emergency departments [5,6,13]. According to Cortese et al. [38], the incidence rate of intussusception solely based on inpatient discharge databases, excluding short stay or emergency department data, could underestimate the true incidence of intussusception by >40%. While previous nationwide studies mainly examined incidence

rates, our study covered all key issues including incidence, post-discharge recurrence, in-hospital recurrence, treatment, clinical outcomes including mortality, and factors associated with disease outcomes of childhood intussusception in children <18 years old in a nationwide complete enumeration scale.

Our study had some limitations. First, the HIRA database of the Korea NHIS is composed of claim data for medical expenses reimbursement, and not originally collected for academic research per se. Therefore, not all clinical information was available, including types of enema reduction, exact site of intussusception, exact time of starting a reduction procedure, histopathology reports for surgical cases, exact time of recurrence within one admission/hospital visit, or laboratory data. Accompanying diagnosis codes in surgical cases of intussusception were identified to presume possible pathologic leading points. However, an accompanying diagnosis in surgical cases might only be an incidental finding rather than a cause of intussusception. Second, a true intussusception incidence was defined as a case with both the intussusception diagnosis code (K561) and a code for enema reduction or a surgical intervention code. Accordingly, patients without claim data for fluoroscopic pneumatic/barium enema or surgical intervention were excluded from data collection, despite having the intussusception diagnosis ICD-10 code (K561). However, as demonstrated by Kohl et al. [39], the incidence rate of intussusception using a retrospective, solely ICD code-based design may significantly overestimate the incidence rate. Therefore, the combination of the ICD-10 code for intussusception and a procedure code for reduction was applied to provide a more specific and clinically relevant case definition [39]. We might have excluded patients who had spontaneous reduction of intussusception such as small-bowel intussusception. However, spontaneous reduction is relatively rare globally (1%), with a very rare occurrence in North America, 2% in Asia, 3% in Europe, and 4% in Oceania [10]. Third, in the present study, direct medical costs did not include non-insurance medical expenses such as ultrasound cost because the HIRA database included medical items covered by the Korea NHIS. Therefore, the real average medical cost of intussusception treatment may be higher than that reported in our study. Lastly, our results were based on Korea NHIS HIRA data between 2007 and 2017 because complete electronic data sets started to be available in 2007. Therefore, we were not able to compare before and after rotavirus vaccination initiation in South Korea, because rotavirus vaccination was introduced in 2007.

Despite the limitations of the claim data for reimbursement used in this study, the Korea NHIS HIRA database enabled us to investigate exact, useful information on childhood intussusception in South Korea with respect to epidemiology, treatment, clinical outcomes, and factors associated with clinical outcomes through complete enumeration over 11 years on a national scale.

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