LIST OF PUBLICATIONS

1) **Khorana J**, Singhavejsakul J, Ukarapol N, Laohapensang M, Wakhanrittee J, Patumanond J. Enema reduction of intussusception: the success rate of hydrostatic and pneumatic reduction. Ther Clin Risk Manag. 2015;11:1837-42.

2) **Khorana J,** Singhavejsakul J, Ukarapol N, Laohapensang M, Siriwongmongkol J, Patumanond J. Prognostic indicators for failed nonsurgical reduction of intussusception. Ther Clin Risk Manag. 2016;12:1231-7.

3) **Khorana J,** Patumanond J, Ukarapol N, Laohapensang M, Visrutaratna P, Singhavejsakul J. Clinical prediction rules for failed nonoperative reduction of intussusception. Ther Clin Risk Manag. 2016;12:1411-6.

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Appendices

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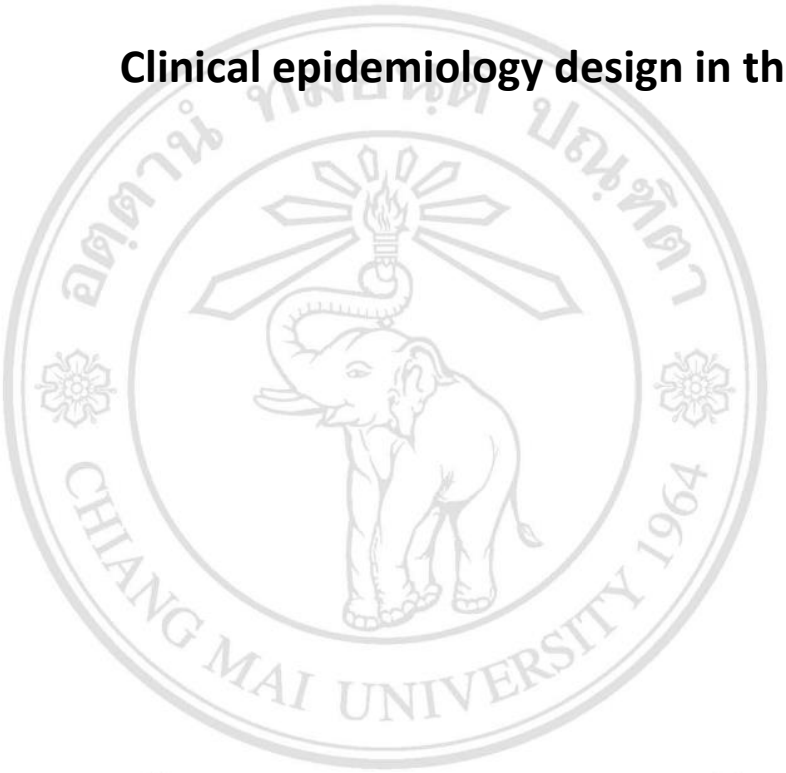
Appendix A

Philosophical context of

Clinical epidemiology design in this thesis



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Philosophical context of clinical epidemiology design in this thesis.

Research questions included in this thesis

1. To compare between hydrostatic and pneumatic reduction, which one has a better success rate?
2. What are the factors that determine the risk of reduction failure of intussusception?
3. Is it possible to construct the simple prediction rule for reduction failure?

Research titles for publication

Study I

Enema reduction of intussusception: the success rate of hydrostatic and pneumatic reduction

Study II

Prognostic indicators for failed nonsurgical reduction of intussusception

Study III

Clinical prediction rules for failed nonoperative reduction of intussusception

1. Theoretical design[1-4]

Clinical epidemiology is the science that mention about how to use the epidemiology in the medical practice. In patient care process, there are many question that can be answer after conducting the researches. The proper research design leads to the accurate and suitable information for clinical practice as well as health care service evaluation.

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1.1 Non-randomized therapeutic efficacy research

In therapeutic efficacy research, the research with randomization is the most reliable such as the randomized controlled trial. In some situation, randomization cannot be done such as the preference of the physician, longer duration for data collection, smaller sample size. Hereby, non-randomized study with well theoretical and statistical design can be done. The question is under a philosophical context of therapeutic efficacy research answers the question “Which treatment is more effective for the therapeutic effect?”

1.1.1 Occurrence relation

Pr(outcome) = f (treatment) | confounders

In the first study the occurrence relation is shown as below which use the causal element of the occurrence relation.

Successful of reduction = f (method of reduction) | Gender + Age+Weight+Vomiting+Abdominal pain+Duration ofsymptom+Rectal bleeding+Dehydration+Hyperthermia+Palpable mass+WBC+Neutrophils+Small bowel obstruction+Ultrasound findings

1.1.2 Propensity score

In non-randomized studies, the treatment group was assigned by nature of disease, physician preference, etc. The systematic differences among treatment groups should be control including confounding by indication and contraindication. Propensity score is one of the methods used for balancing the confounders between treatments group in the same score.

In study I, the propensity score was used to adjust all the factors.The propensity score was generated by logistic regression to estimate the probability of the choice of the method of reduction (pneumatic vs barium).

Propensity Score = Pr (method of treatment |sex, age group of 36 months, weight group of 8 kg, duration of symptoms for 48 hours, vomiting, abdominal pain, rectal bleeding, diarrhea, abdominal distension, constipation, temperatureof 37.8°C, palpable abdominal mass, location of the mass, white blood cell count of 10,000/mm3, plain abdominal radiography showing bowel obstruction, and ultrasound showing poor prognostic sign)

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Then, the propensity score was used instead of the confounders in the design.

Pr**(Successful of reduction)**= f **(method of reduction)**| **Propensity score**

1.2 Prognostic research

Prognostic research is one of three components of clinical practice that are diagnosis, prognosis and treatment. There are three dimensions of prognostic research depending on the

objective of the study. Those are the prognosis of outcome of disease, cause of undesirable disease outcome and prediction of undesirable outcome. The question is under a philosophical context of prognostic research answers the question “What are prognostic factors of event occurrence?”

1.2.1 Occurrence relation

Incidence (outcome) = f (d1 + d2 + …)

In the second study the occurrence relation is shown as below and used this model in predicting of undesirable outcome dimension.This study use the descriptive element of the occurrence relation.

Failure reduction = f (Gender+ Age+Weight+Vomiting+Abdominal pain+Duration of symptom+Rectal bleeding+ Dehydration+ Hyperthermia+Palpable mass+ Small bowel obstruction+Ultrasound findings)

1.3 Clinical prediction rule

A clinical prediction rule is derived from the analysis of various predictors to predict the clinical outcome. Predictors is the clinical data of the patients including patient profile and routine investigation. The clinical prediction rule can be constructed for diagnosis and prognosis study. The objective of the rules are aided in clinical decision.

1.3.1 Occurrence relation

Pr(outcome y) = f(Clinical profiles+ non-clinical profiles+ index test)

In the third study the occurrence relation is shown as below and used this model in prognosis prediction rules.This study also use the descriptive element of the occurrence relation.

Failure reduction = f (Gender+ Age+Weight+Vomiting+Abdominal pain+Duration of symptom+Rectal bleeding+ Dehydration+ Hyperthermia+Palpable mass+ Small bowel obstruction+Ultrasound findings)

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2. Data collection design

2.1 Study setting and period

All studies in this thesis was the retrospective cohort study in Chiang Mai University Hospital and Siriraj Hospital.The data were obtained by chart review and electronic databasesfrom January 2006 to December 2012.

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2.2 Data collection process

The data collection process was shown in Table below.

Data collection process	Study I	Study II	Study III
Data collection scheme			
- Determinant-Outcome time - Construction of the population - Determinant assignment	>0 Population Observation	>0 Population Observation	>0 Population Observation
Domain	Intussusception patient who age 0-15 year	Intussusception patient who age 0-15 year	Intussusception patient who age 0-15 year
Contrast group	**Intervention A** pneumatic reduction **Intervention B** hydrostatic reduction	**Index group** Failed reduction **Comparison group** Successful reduction	**Index group** Failed reduction **Comparison group** Successful reduction
Event	Outcome of reduction : focused on successful of reduction	Outcome of reduction : focused on failed reduction	Outcome of reduction : focused on failed reduction

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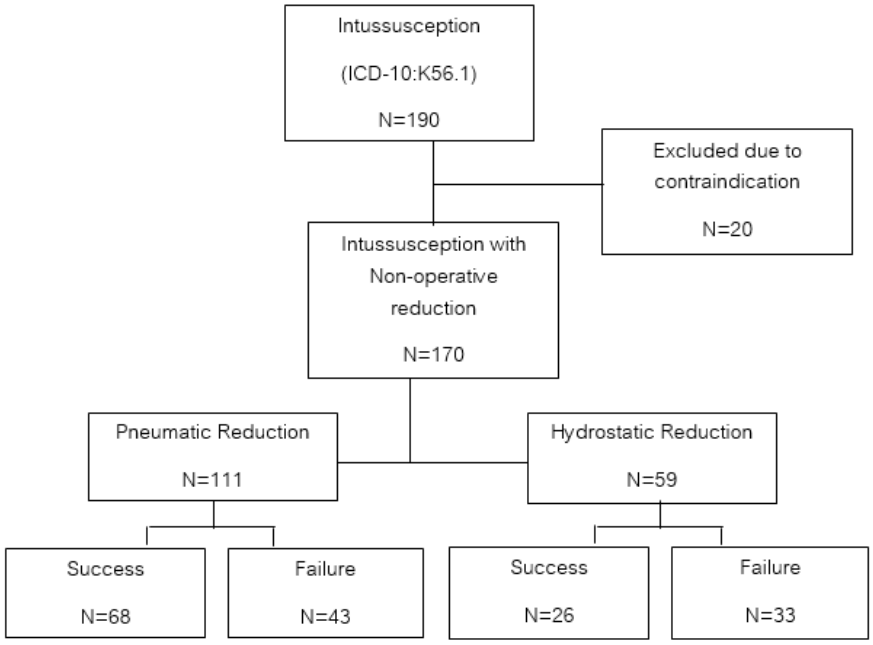
2.3 Study flow

The study flow diagram of all three studies is shown below.

Study I



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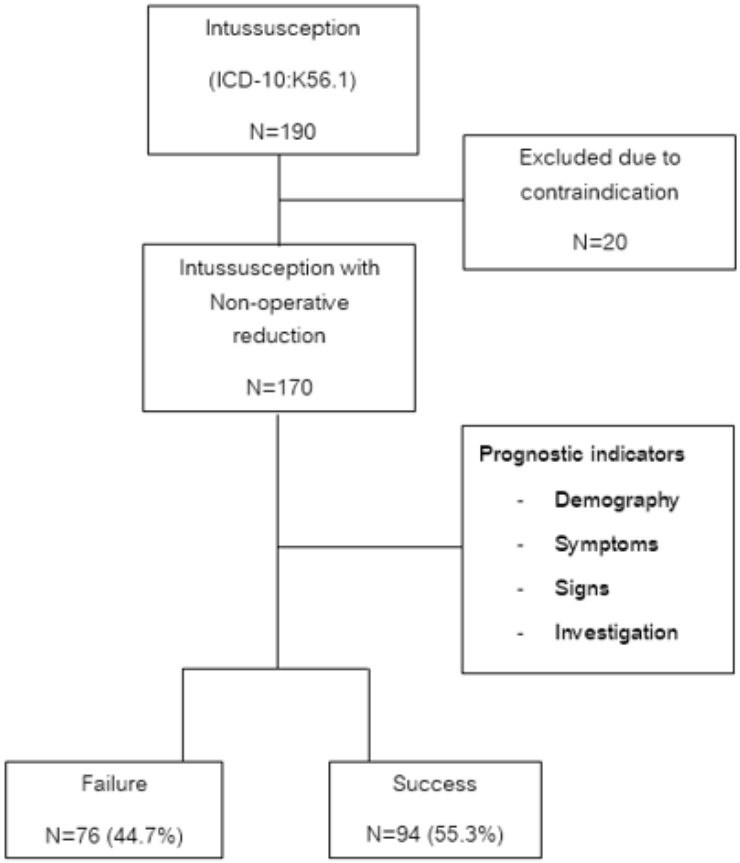
Study II, III



3. Data analysis design

3.1 Non-randomized therapeutic efficacy research : Study I

Step1:

Analysis of baselinedemographic data of patients with intussusception (patient factors, symptoms, signs and investigation) were done. The categorical descriptive data was reported in count and percent. The categorical univariable analysis was done by Fisher's exact test. The numerical descriptive data was reported in mean and standard deviation. The numerical univariable analysis was done by student's t-test or Mann–Whitney U test.

Step 2:

The propensity score of the previously mention determinants was done by logistic regression. The figure below shows the score overlapping in two treatment groups.

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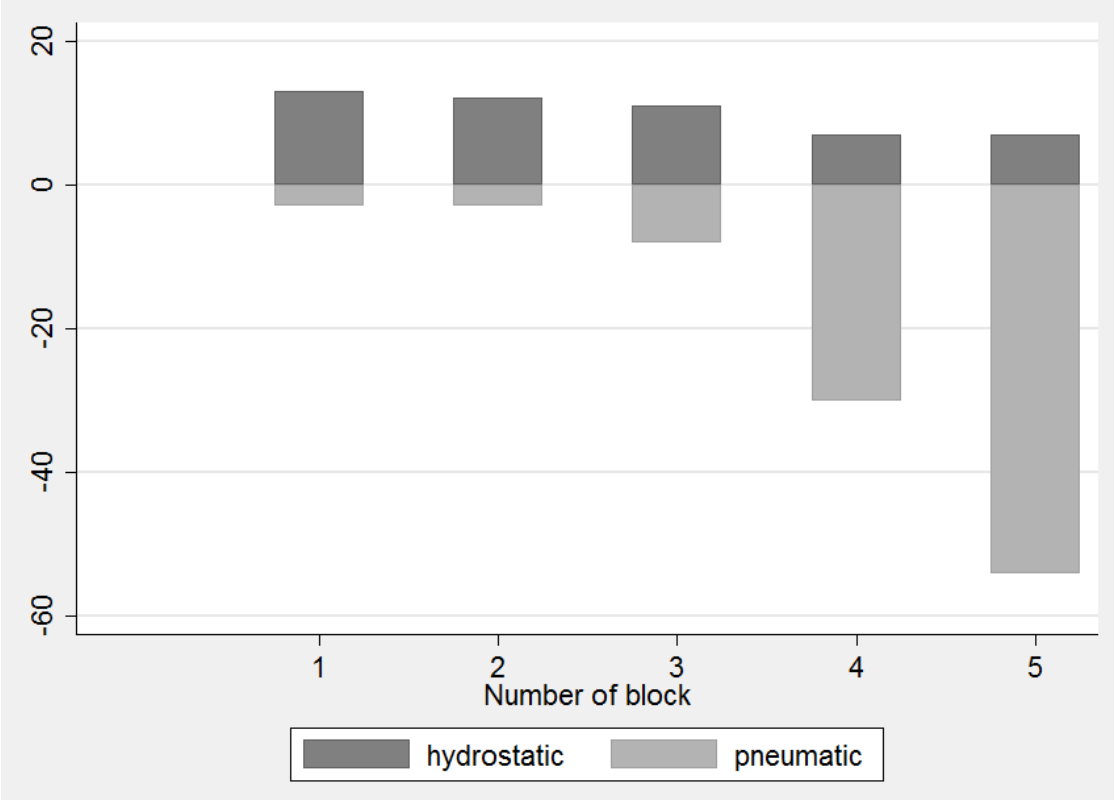

Step 3:

The multivariable regression analysisfor the successful reduction between pneumatic and barium reduction adjusted by propensity score was exponential risk regression. Statistical significance level was set as two-tailed with P-value <0.05.

3.2 Prognostic research : Study II

Step 1:

The descriptive data was reported in count and percent for categorical data, mean and standard deviation or median and interquartile range for continuous data. The univariable analysis was done by Fisher's exact test in categorical data and student's t-test or Mann–Whitney U test in continuous data.

Step 2:

The multivariable regression analysis for the prognostic factors of failure reduction of intussusception was done by generalized linear model for exponential risk regression and reported by risk ratio (RR) clustering by age of 3.Cluster analysis[5] is a method to identify a meaningful allocation of observations in group which high similarity within group and low

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similarity between groups. The analysis of the observations within the same cluster are comparable. Our second study was used cluster by age of 3 years in order to compare the children with intussusception with different nature of disease. The pathologic leading point was more commonly found in children age more than 3 years.

Step 3:

The receiver operating characteristic (ROC) curve was used for detecting the performance of the multivariable model. The statistical significance level was set as two-tailed with a P-value <0.05.

3.3 Clinical prediction rule : Study III

Step 1:

Analysis of the ten significant predictors for failed non-surgical reduction derived from the second study was done. Numerical factors such as bodyweight, duration of symptoms and temperature were divided in two groups. The cut-off points were determined from the values that yielded all statistically significant regression coefficients and the highest area under the receiver operating characteristic (ROC) curve of the logistic regression model. The data were presented in count and percentage. The univariable comparative statistics were done by Fisher's exact test for categorical data.

Step 2:

Generalized linear model for exponential risk regression clustering by the age of 3 years (due to the risk for pathologic leading point) was used for multivariable analysis.

Step 3:

The regression coefficients of each factor were transformed to item scores. All item scores were added together for a total score. The total scores were used as a predictor for failed non-surgical reduction of intussusception.

Step 4:

The risk level was to categorize total scores into a low risk group and a high risk group. The cut-off points for the total scores were determined from the values that yielded the lowest likelihood ratio of positive for failed reduction in the low risk group and highest likelihood ratio of positive for failed reduction in the high risk group. The statistical significance level was set as two-tailed with a P-value <0.05.

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Step 5:

The receiver operating characteristic (ROC) curve was used for detecting the performance of the multivariable score model. The statistical significance level was set as two-tailed with a P-value <0.05.

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Appendix B

Khorana J, Singhavejsakul J, Ukarapol N, Laohapensang M, Wakhanrittee J, Patumanond J. Enema reduction of intussusception: the success rate of hydrostatic and pneumatic reduction. TherClin Risk Manag. 2015;11:1837-42.

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Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Enema reduction of intussusception: the success rate of hydrostatic and pneumatic reduction

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Purpose: Intussusception is a common surgical emergency in infants and children. The incidence of intussusception is from one to four per 2,000 infants and children. If there is no peritonitis, perforation sign on abdominal radiographic studies, and nonresponsive shock, nonoperative reduction by pneumatic or hydrostatic enema can be performed. The purpose of this study was to compare the success rates of both the methods.

Methods: Two institutional retrospective cohort studies were performed. All intussusception patients (ICD-10 code K56.1) who had visited Chiang Mai University Hospital and Siriraj Hospital from January 2006 to December 2012 were included in the study. The data were obtained by chart reviews and electronic databases, which included demographic data, symptoms, signs, and investigations. The patients were grouped according to the method of reduction followed into pneumatic reduction and hydrostatic reduction groups with the outcome being the success of the reduction technique.

Results: One hundred and seventy episodes of intussusception occurring in the patients of Chiang Mai University Hospital and Siriraj Hospital were included in this study. The success rate of pneumatic reduction was 61% and that of hydrostatic reduction was 44% (P=0.036). Multivariable analysis and adjusting of the factors by propensity scores were performed; the success rate of pneumatic reduction was 1.48 times more than that of hydrostatic reduction (P=0.036, 95% confidence interval [CI] =1.03–2.13).

Conclusion: Both pneumatic and hydrostatic reduction can be performed safely according to the experience of the radiologist or pediatric surgeon and hospital setting. This study showed that pneumatic reduction had a higher success rate than hydrostatic reduction.

Keywords: intussusception, pneumatic reduction, hydrostatic reduction, success rate

Introduction

Intussusception is a common surgical emergency in infants and children. The incidence of intussusception is approximately one to four per 2,000 infants and children.[1] The diagnosis of intussusception was confirmed by clinical and radiological findings. Common signs and symptoms included colicky abdominal pain, vomiting, palpable abdominal mass, and currant jelly stool. A plain abdominal X-ray might show a soft tissue mass, target sign, meniscus sign, and absence of air in ascending colon, and/or small-bowel dilatation.[2] The ultrasound to diagnose intussusception was performed from the findings of the doughnut and pseudokidney signs that indicate the bowel-in-bowel condition characteristic of the intussusception.[3]

According to the Brighton Collaboration Intussusception Working Group,[4] the case definition of intussusception is given as the invagination of one segment of intestine into a segment of distal intestine. The level 1 diagnosis certainties are the surgical, and/or radiologic, and/or autopsy criteria. The level 2 diagnostic certainty is the clinical criteria which include two major criteria or one major with three minor

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criteria. The diagnostic major criteria consist of the evidence of intestinal obstruction, intestinal invagination, and intestinal vascular compromise or venous congestion. The minor criteria are the predisposing factors (age <1 year, male sex), abdominal pain, vomiting, lethargy, pallor, hypovolemic shock, and abnormal nonspecific bowel gas pattern in abdominal radiograph.[4]

All of the cases that met the radiologic criteria were reviewed. After the case of intussusception was diagnosed, the method of treatment was chosen. The modality of treatments consisted of operative and nonoperative management. Contraindications for nonoperative management were hemodynamic instability, peritonitis, and/or abdominal signs of perforation on abdominal X-ray. Without contraindications, nonoperative methods included performing hydrostatic or pneumatic reduction. A previous literature review[5] of the success rates of both methods in another care unit showed significant differences. The hydrostatic reduction could be performed by the use of saline, barium, or another solution. The overall success rate of the nonoperative reduction ranged from 46% to 94% according to a review by Bekdash et al.[5]

In this study, we were interested in comparing the success rates of the hydrostatic and pneumatic reduction techniques. Air reduction was represented pneumatic reduction and barium reduction represented hydrostatic reduction. The comparative study of the success of both methods was done.

Methods

This retrospective cohort study was approved by the Ethics Committee of Chiang Mai University Hospital and Siriraj Hospital. The data were obtained by chart review and electronic databases. Patient consent was not required in this retrospective study. All intussusception patients (ICD-10 code K56.1) who had visited Chiang Mai University Hospital and Siriraj Hospital from January 2006 to December 2012 were included in the study. The data collected included demographic data (sex, age, and bodyweight), symptoms (vomiting, abdominal pain, rectal bleeding, diarrhea, distention, constipation, and duration of symptoms), signs (temperature, palpable mass, and location of the mass), and investigations (white blood cell counts, neutrophils, electrolytes, abdominal radiography, and ultrasound findings). Specific radiography findings showed small-bowel obstruction and ultrasound showed poor prognostic signs such as thick peripheral hypoechoic rim, free intraperitoneum fluid, fluid trapped within intussusception, enlarged lymph node in intussusception, pathologic leading point, absence of blood flow in the intussusception.[1] Based on the methods of reduction used for treatment, the patients were grouped as pneumatic reduction group and barium reduction group. The outcome of the study was the success of nonoperative reduction.

We included all intussusception patients aged 0–15 years and excluded the patients who had contraindications for nonoperative reductions, which included peritonitis, perforation sign on abdominal radiographic study, and nonresponsive shock that required surgery.

The nonoperative methods followed were pneumatic reduction and barium reduction. These procedures were performed in well-hydrated children. The standard techniques of reduction comprised three repeated attempts of 3 minutes each. In Chiang Mai University Hospital, all patients received pneumatic reduction performed by a radiologist under fluoroscopic guidance. In Siriraj Hospital, pneumatic reduction was performed by a pediatric surgeon under ultrasound guidance and barium reduction was performed by a radiologist under fluoroscopic guidance. A Foley catheter was inserted via the anus of the patients and the buttocks were taped to prevent air or barium leakage. For the pneumatic reduction method, all patients received air pressure from 80 to 120 mmHg. For the barium reduction method, the barium bucket was hung 3 feet above the patients. Sedation drugs were given according to it's hospital sedation guidelines.

The success of reduction was determined by the disappearance of intussusception and the visualization of barium or air from cecum to ileum through ileocecal valve, or barium- or air-distended ileum and absence of intussusception after reduction by ultrasound examination.[6]

The statistical analysis was done by using commercial statistical software (STATA 11.0; StataCorp LP, College Station, TX, USA). The categorical descriptive data were reported as counts (N) and percentage (%). The categorical univariable analysis was done by Fisher's exact test. The numerical descriptive data were reported as mean and standard deviation. The numerical univariable analysis was done by Student's *t*-test or Mann–Whitney *U*-test. Many factors influence the failure of reduction techniques. It was reported that duration of symptoms, emesis, bloody stool, location of intussusception, and poor prognosis sign on ultrasound were associated with failure reduction.[7] The propensity score was used to adjust all the factors, which included sex, age group of 36 months, weight group of 8 kg, duration of symptoms for 48 hours, vomiting, abdominal pain, rectal bleeding, diarrhea, abdominal distension, constipation, temperature

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Table 1 Baseline characteristics of all children with intussusceptions in Chiang Mai University Hospital and Siriraj Hospital from 2006 to 2012 (all 190 cases)

Characteristics	N	%
Patient factors		
Sex		
Male	128	67.37
Female	62	32.63
Age (month)[a]	9	7–16
Weight (kg)[b]	9.73	4.22
Symptoms		
Vomiting	166	87.37
Abdominal pain	147	77.37
Duration of symptoms (hours)[a]	24	20–48
Rectal bleeding	135	71.05
Distension	96	50.53
Diarrhea	32	16.84
Constipation	21	11.05
Signs		
Temperature (°C)[b]	37.34	0.69
Palpable mass	123	64.74

Notes: [a]Median, interquartile range; [b]mean, standard deviation.

Table 2 Investigation, treatment, and outcome of all children with intussusceptions in Chiang Mai University Hospital and Siriraj Hospital from 2006 to 2012 (all 190 cases)

Characteristics	N	%
Investigations		
WBC count (/mm^3)[a]	12,000	9,030–15,800
Neutrophils (%)[b]	56.56	16.78
Na (mmol/L)[b]	136.67	4.26
Ultrasound (poor prognosis sign)	76	45.24
Location		
Right lower quadrant	17	9.34
Right upper quadrant	101	55.49
Left upper quadrant	33	18.13
Left lower quadrant	29	15.93
In rectum	2	1.10
Treatment		
Surgical (presence of contraindication for nonsurgical reduction)	20	10.53
Nonsurgical (170 cases)	170	89.47
Pneumatic reduction	111	65.29
Hydrostatic reduction	59	34.71
Outcome (170 cases)		
Successful reduction	94	55.29

Notes: [a]Median, interquartile range; [b]mean, standard deviation.
Abbreviation: WBC, white blood cell count.

of 37.8°C, palpable abdominal mass, location of the mass, white blood cell count of 10,000/mm^3, plain abdominal radiography showing bowel obstruction, and ultrasound showing poor prognostic sign by logistic regression. The propensity score was generated to estimate the probability of the choice of the method of reduction (pneumatic vs barium). The success of reduction was measured by risk ratio. A multivariable exponential risk regression analysis was performed to determine the success rates of two methods of reduction that were adjusted by propensity score. Statistical significance level was set as two-tailed with P-value <0.05.

Results

A total of 190 episodes of intussusception were identified among patients who visited Chiang Mai University Hospital and Siriraj Hospital. The summary of the epidemiological characteristics of all the patients are shown in Tables 1 and 2. Twenty patients were excluded due to contraindications and surgery after the diagnosis. One hundred and seventy episodes were included in this study (Figure 1). The male

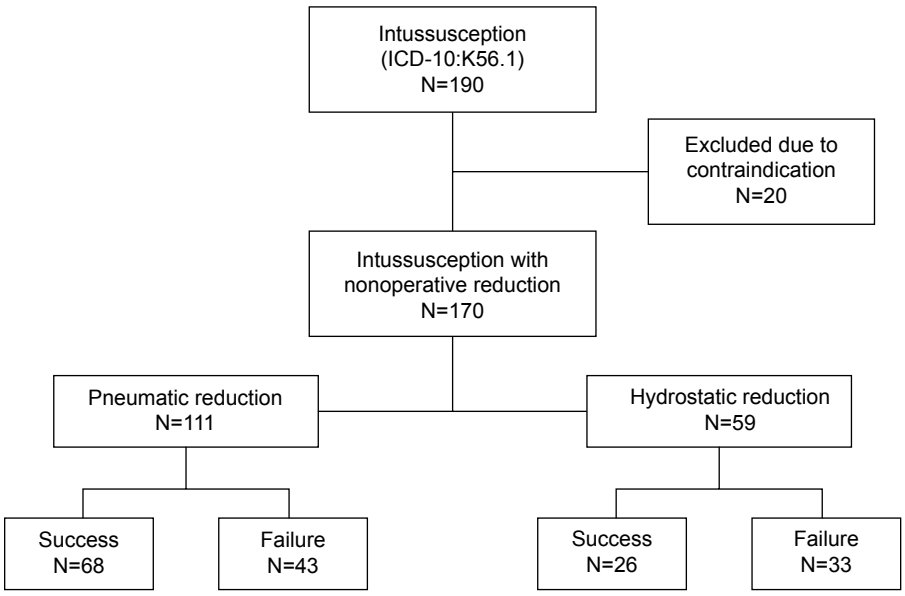

Figure 1 Study flow of pneumatic and barium reduction.

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Table 3 Baseline characteristics of children with intussusceptions who received nonoperative reduction by pneumatic reduction (n=111) and hydrostatic reduction (n=59)

Characteristics	Pneumatic reduction, n (%)	Hydrostatic reduction, n (%)	*P*-value
Patient factors			
Sex			
Male	75 (65.79)	39 (34.21)	0.865
Female	36 (64.29)	20 (35.71)	
Age (month)[a]	10 (7–16)	8 (6–18)	0.449
Weight (kg)[b]	9.23 (3.16)	9.89 (3.46)	0.211
Symptoms			
Vomiting	96 (65.31)	51 (34.69)	1.000
Abdominal pain	85 (62.96)	50 (37.04)	0.237
Duration of symptoms (hours)[a]	24 (19–48)	36 (24–48)	0.119
Rectal bleeding	76 (63.87)	43 (36.13)	0.601
Distension	41(52.56)	37 (47.44)	0.002
Diarrhea	19 (67.86)	9 (32.14)	0.831
Constipation	14 (77.78)	4 (22.22)	0.008
Signs			
Temperature (°C)[b]	37.19 (0.70)	37.47 (0.57)	0.009
Palpable mass	76 (67.26)	37 (32.74)	0.497

Notes: [a]Median (interquartile range); [b]mean (standard deviation).

to female ratio was 2:1. The median age of the patient was 9 months with a mean weight of 9.5 kg. The most common symptoms were vomiting, abdominal pain, and rectal bleeding (86.5%, 79.4%, and 70%, respectively). Diarrhea was found in 16.5% and constipation was found 10.6% of the patients. A palpable abdominal mass and abdominal distension were observed in 66.5% and 45.9% of the patients, respectively. The median duration of symptoms before presentation was 24 hours. Twenty two percent of the patients had fever. Plain abdominal radiography showed small-bowel obstruction in 66.9% of the patients. The ultrasonography before reduction showed at least one of the poor prognostic signs, as mentioned in the "Methods" section, in 43.9% of the patients. The most common location of the palpable mass was right upper quadrant and was found in 58% of the patients. The overall success rate in this study was 55.3%. The patients were divided into the pneumatic reduction group (111 patients) and the barium reduction group (59 patients). Comparison between the two groups is shown in Tables 3 and 4. Univariable analysis showed that the success rate of

Table 4 Investigation of children with intussusceptions who received nonoperative reduction by pneumatic reduction (n=111) and hydrostatic reduction (n=59)

Characteristics	Pneumatic reduction, n (%)	Hydrostatic reduction, n (%)	*P*-value
Investigations			
WBC count (/mm^3)[a]	12,675 (9,260–17,040)	10,830 (8,600–14,570)	0.079
Neutrophils (%)[b]	57.31 (17.07)	54.83 (15.63)	0.365
Na (mmol/L)[b]	137.51 (3.89)	136.05 (4.41)	0.031
K (mmol/L)[b]	4.41 (4.02)	3.84 (0.65)	0.289
Cl (mmol/L)[b]	104.52 (0.48)	100.95 (5.53)	<0.001
Total CO_2 (mmol/L)[b]	19.42 (2.95)	19.5 (4.55)	0.895
Location			0.117
Right lower quadrant	6 (40.00)	9 (60.00)	
Right upper quadrant	66 (68.04)	31 (31.96)	
Left upper quadrant	21 (67.74)	10 (32.26)	
Left lower quadrant	17 (73.91)	6 (26.09)	
In rectum	0 (0.00)	1 (100.00)	
Plain abdominal X-ray (small-bowel obstruction)	65 (60.75)	42 (39.25)	0.026
Ultrasound (poor prognosis sign)	11 (16.18)	57 (83.82)	0.001

Notes: [a]Median (interquartile range); [b]mean (standard deviation).
Abbreviation: WBC, white blood cell count.

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Table 5 Outcome of children with intussusceptions who received nonoperative reduction by pneumatic reduction (n=111) and hydrostatic reduction (n=59)

Characteristics	Success rate, n (%)	Failure, n (%)	*P*-value
Method of reduction			0.036
Pneumatic reduction	68 (61.26)	43 (38.74)	
Hydrostatic reduction	26 (44.07)	33 (55.93)	

pneumatic reduction (61%) was significantly higher than that of barium reduction (44%) (*P*-value =0.036). The propensity score was used to control all the variables. The success rate of pneumatic reduction was 1.48 times more than that of barium reduction (*P*-value =0.036, confidence interval [CI] =1.03–2.13) as shown in Tables 5 and 6. Perforation after reduction was found in only one pneumatic reduction case, and the patient safely received a right hemicolectomy due to colonic gangrene and perforation.

Discussion

The modalities for the management of intussusception included nonoperative and operative management. The patient with no contraindication received nonoperative management as the initial treatment. The choices available for nonoperative treatment of intussusception were hydrostatic and pneumatic reduction.

In 1885, intussusception was treated with laparotomy and had a high mortality rate of 70%. Treves also had some idea of reduction, but did not establish the rule. The rule of reduction might set for the pressure used and the time used for each attempts.[8] In 1935, Hipsley used hydrostatic pressure to reduce intussusception and proposed the technique of pressure reduction.[9] By that time, the reductions were performed hydrostatically. In 1986, a large intussusception study in People's Republic of China including 6,396 cases over a 13-year period were successfully reduced by air reduction with a success rate of 95%.[10] After that, there was a worldwide increase in the use of pneumatic reduction. Both hydrostatic and pneumatic reduction techniques had been performed in cases of feasibility in some health care institutes. Also, in Thailand, in 2011, Kruatrachue et al reported a switch from barium to air reduction since 1992 with the success rate of 68%.[11] In 2013, Bekdash et al collected results from series reports regarding the success rate of intussusception reduction to establish an index of successful reduction.[5] This recruited study used both air and barium for reduction depending on the radiologist or pediatric surgeon's preference, experience, and institutional setting. There were not many comparative studies between the success rate of hydrostatic and pneumatic reduction in the literature. In 2013, Fallon et al studied the risk factors for surgery in patients with intussusception and found that hydrostatic enema was a predictor for failed nonoperative reduction in univariable analysis.[12] In another collective review in 2004, Daneman and Navarro found that the success rate of pneumatic reduction was 51%–100% and that of hydrostatic reduction was 12.5%–95.5%.[13]

In this retrospective analysis, we found that the overall success rate was ~55%. The pneumatic reduction technique showed a success rate of 61% and hydrostatic reduction technique 44%. The results of our two institutional studies did not show a high success rate, which may be due to the symptom duration before hospital admission being quite a long period of time. Some of the cases were referred from remote provincial hospitals and patients had to travel long distances to receive treatment. We compared the result of pneumatic and hydrostatic reduction by multivariable analysis controlling the factors by the use of propensity score. So, the results of both the methods of reduction were adjusted to allow for comparison. The risk factors associated with failure of the reduction methods will be analyzed in future studies. The complication usually observed in both the methods was perforation after reduction, which was reported as 0%–5.9% in a previous study.[13] Our study did not focus on the complications but focused on the success rate. We found that <1% of our study population sustained a perforation after reduction. Hence, the complication rates and the surgical findings will be discussed in the future studies.

Conclusion

The method of nonoperative reduction of intussusception was dependent on the experience of the radiologist or pediatric surgeon and the hospital setting. We found the success rate of pneumatic reduction was 1.48 times more than that of barium reduction in this study. Both methods can be performed safely before operation if there are no contraindications. The risk

Table 6 Multivariable risk ratio of successful reduction of intussusception adjusted by propensity score

Characteristics	Crude relative risk (95% confidence interval)	*P*-value	Multivariable risk ratio (95% confidence interval)	*P*-value
Method of reduction (pneumatic over hydrostatic)	1.39 (0.88–2.18)	0.153	1.48 (1.03–2.13)	0.036

factors associated with the failure of reduction methods will be included in our next study.

Disclosure

The authors report no conflicts of interest in this work.

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Appendix C

Khorana J, Singhavejsakul J, Ukarapol N, Laohapensang M, Siriwongmongkol J, Patumanond J. Prognostic indicators for failed nonsurgical reduction of intussusception. TherClin Risk Manag. 2016;12:1231-7..

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ORIGINAL RESEARCH

Prognostic indicators for failed nonsurgical reduction of intussusception

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Purpose: To identify the risk factors for failure of nonsurgical reduction of intussusception.

Methods: Data from intussusception patients who were treated with nonsurgical reduction in Chiang Mai University Hospital and Siriraj Hospital between January 2006 and December 2012 were collected. Patients aged 0–15 years and without contraindications (peritonitis, abdominal X-ray signs of perforation, and/or hemodynamic instability) were included for nonsurgical reduction. The success and failure groups were divided according to the results of the reduction. Prognostic indicators for failed reduction were identified by using generalized linear model for exponential risk regression. The risk ratio (RR) was used to report each factor.

Results: One hundred and ninety cases of intussusception were enrolled. Twenty cases were excluded due to contraindications. A total of 170 cases of intussusception were included for the final analysis. The significant risk factors for reduction failure clustered by an age of 3 years were weight <12 kg (RR =1.48, P=0.004), symptom duration >3 days (RR =1.26, P<0.001), vomiting (RR =1.63, P<0.001), rectal bleeding (RR =1.50, P<0.001), abdominal distension (RR =1.60, P=0.003), temperature >37.8°C (RR =1.51, P<0.001), palpable abdominal mass (RR =1.26, P<0.001), location of mass (left over right side) (RR =1.48, P<0.001), poor prognostic signs on ultrasound scans (RR =1.35, P<0.001), and method of reduction (hydrostatic over pneumatic) (RR =1.34, P=0.023). The prediction ability of this model was 82.21% as assessed from the area under the receiver operating characteristic curve.

Conclusion: The identified prognostic factors for the nonsurgical reduction failure may help to predict the reduction outcome and provide information to the parents.

Keywords: intussusception, pneumatic reduction, hydrostatic reduction, prognostic indicators, failure rate

Introduction

Intussusception is a frequent cause of bowel obstruction in infants and preschool children. Its incidence has been found to be one to four per 2,000 infants and children worldwide.[1] Intussusception is defined as the invagination of one segment of intestine into a segment of distal intestine. The diagnosis of intussusception is done according to the Brighton Collaboration Intussusception Working Group criteria.[2] Treatment includes both nonsurgical and surgical procedures; the two methods of nonsurgical reduction are hydrostatic and pneumatic. Nonsurgical reduction can be done safely if there are no contraindications. Absolute contraindications such as peritonitis, perforation, and dehydration lead to nonresponsive shock.[3] Surgical treatment is necessary in cases with contraindications or failed nonsurgical reduction.

Nonsurgical reduction failure is defined as intussusception that could not be reduced nonoperatively. The timeout limit of nonoperative reduction is defined in the "Materials and methods" section. The success rate of the nonsurgical reduction has

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been found to range from 46% to 94%.[4] In our previous series, a study on the enema reduction of intussusception was found to have an overall success rate of 55.3% which was quite low compared with the other studies in the same series.[5] So, this study was conducted to identify the causes of reduction failure. Many factors influence failed reductions. The duration of symptoms, emesis, bloody stool, poor prognosis sign on ultrasound scans (a thick peripheral hypoechoic rim, free intraperitoneum fluid, fluid trapped within intussusceptum, enlarged lymph node in intussusception, pathologic leading point, and absence of blood flow in the intussusception),[1] and age group[6] were found to be associated with failed reduction in the previous study.[7] We aimed to predict the determinants of nonsurgical reduction failure.

Materials and methods

This retrospective cohort study was approved by the Ethics Committee of Chiang Mai University Hospital (CMU) and Siriraj Hospital (SI). According to the retrospective study, the Ethical committees of CMU and SI did not require patient consent. This study was a part of a series of studies on intussusception. Data from intussusception patients (International Classification of Diseases, Tenth Edition, code K56.1) who were treated with nonsurgical reduction in CMU and SI between January 2006 and December 2012 were collected. The inclusion criterion included the presence of intussusception, an age of 0–15 years, and the absence of contraindications for nonsurgical reduction. Absolute contraindications were peritonitis, abdominal X-ray signs of perforation, and/or hemodynamic instability. The chart and electronic database reviews were conducted to collect information on demographics, symptoms, signs, and investigations (sex, age, bodyweight, vomiting, abdominal pain, rectal bleeding, diarrhea, distention, constipation, duration of symptoms, temperature, palpable mass, location of the mass, white blood cell counts, neutrophils, electrolytes, abdominal radiography, and ultrasound findings). Specific radiographic findings included small bowel obstruction. Poor prognostic signs on ultrasound scans were counted if one of the signs mentioned was present. The patients were divided into a success group and a failure group according to the results of the nonsurgical reduction.

The standard nonsurgical reduction technique was performed in the patients who had no contraindications. The pneumatic reduction was performed by a radiologist under fluoroscopic guidance (in CMU) or by a pediatric surgeon under ultrasound guidance (in SI). The barium reduction was done by radiologist under fluoroscopic guidance (in SI). After resuscitation of the infants or children, nonsurgical reduction was done. In pneumatic reduction, we used the pressure enema from 80 to 120 mmHg with three attempts of 3 minutes each. In barium reduction, we controlled the pressure enema by limiting the height of the barium bucket to not >3 ft above buttocks with three attempts of 3 minutes each. We sedated the patients as appropriate. Failed reduction was defined by a remaining intussusception mass where barium or air could not pass from the cecum to the ileum through the ileocecal valve after the reduction procedure.[8]

Statistical analysis was done with commercial statistical software (STATA 11.0; StataCorp LP, College Station, TX, USA). The descriptive data were reported in count and percent for categorical data, and mean and standard deviation or median and interquartile range for continuous data. The univariable analysis was done by Fisher's exact test for categorical data and Student's *t*-test or Mann–Whitney *U*-test for continuous data. The multivariable regression analysis of the prognostic factors for intussusception reduction failure was done by generalized linear model for exponential risk regression, and reported by risk ratio (RR) clustered by an age of 3 years (due to the risk for pathologic leading point).[9] The receiver operating characteristic curve was plotted for assessing the performance of the multivariable model. The statistical significance level was set as two-tailed with a *P*-value <0.05.

Results

One hundred and seventy intussusception patients in CMU and SI received nonsurgical reduction. The overall failure rate was 44.7% (Figure 1). The factors that influenced

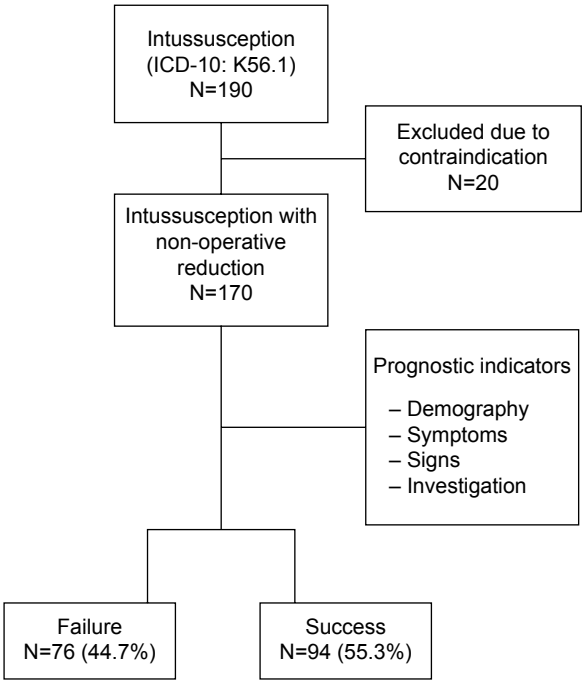

Figure 1 Flow of the study.
Abbreviation: ICD-10, International Classification of Diseases, Tenth Edition.

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the failure of nonsurgical reduction were analyzed by the univariable analysis (Tables 1 and 2) and multivariable analysis (Table 3). In the univariable model, the significant factors for failure of the reduction of intussusception analyzed were age, bodyweight, vomiting, rectal bleeding, abdominal distension, constipation, temperature, location of mass, serum sodium, small bowel obstruction in the abdominal radiography, and method of reduction (*P*-value for each parameter are stated in Tables 1 and 2). After multivariable analysis was done, we found that the significant risk factors for failure reduction clustered by an age of 3 years were weight <12 kg (RR =1.48, *P*=0.004), symptom duration >3 days (RR =1.26, *P*<0.001), vomiting (RR =1.63, *P*<0.001), rectal bleeding (RR =1.50, *P*<0.001), abdominal distension (RR =1.60, *P*=0.003), temperature >37.8°C (RR =1.51, *P*<0.001), palpable abdominal mass (RR =1.26, *P*<0.001), location of mass (left over right side) (RR =1.48, *P*<0.001), poor prognostic signs on ultrasound scans (RR =1.35, *P*<0.001), and method of reduction (hydrostatic over pneumatic) (RR =1.34, *P*=0.023). The receiver operating characteristic curve was plotted to assess the prediction ability of this model of the described risk factors for the failed reduction as shown in Figure 2. An area under curve of 82.21% was obtained.

Nonsurgical reductions failed in 76 patients. All those patients were operated. The operative findings of the intussusception patients with failed nonoperative reduction are shown in Figure 3. A pathologic finding of resection and anastomosis group was the necrosis of the bowel. The pathologic leading points were found in six patients. The pathologic leading points reported were jejunal polyp, B-cell lymphoma, ileal diverticulitis, and Meckel's diverticulum (in two patients).

Table 1 Baseline characteristics (demographics and symptoms) of children with failed (n=76) and successful (n=94) nonsurgical reduction of intussusception

Characteristics	Failed, n (%)	Successful, n (%)	*P*-value
Demography			
Sex			1.000
Male	51 (44.74)	63 (55.26)	
Female	25 (44.64)	31 (55.26)	
Age (months)[a]	8 (6–11)	12 (7–23)	<0.001
Weight (kg)[b]	8.61 (1.98)	10.15 (3.90)	0.002
Symptoms			
Vomiting	71 (48.30)	76 (51.70)	0.023
Abdominal pain	56 (41.48)	79 (58.52)	0.127
Duration of symptoms (hours)[a]	24 (24–48)	24 (18–48)	0.155
Rectal bleeding	65 (54.62)	54 (45.38)	<0.001
Distension	48 (61.54)	30 (38.46)	<0.001
Diarrhea	12 (42.86)	16 (57.14)	1.000
Constipation	4 (22.22)	14 (77.78)	0.048

Notes: [a]Presented as median (interquartile range). [b]Presented as mean (standard deviation).

Discussion

This study was the second in a series of studies on intussusception conducted in our two institutions. The first study explored the success rate of the pneumatic and hydrostatic reduction. We found that the success rate of nonsurgical reduction was 55.3%.[5] So, this study was set to identify the factors that lead to failed reduction.

The significant risk factors identified in our study were weight <12 kg, symptom duration >3 days, vomiting, rectal bleeding, abdominal distension, temperature >37.8°C, palpable abdominal mass, location of mass (left over right side), poor prognostic signs on ultrasound scans, and method of reduction (hydrostatic over pneumatic).

The duration of symptoms associated with failed reduction remains controversial. In previous studies, different results were obtained regarding this issue. Reijnen et al stated that a duration of symptoms of >48 hours was a significant predictor of failure of hydrostatic reduction.[10] Chung et al studied about the risk factors leading to surgical reduction and found that the long-standing duration of illness (>24 hours) was a primary factor. In that series, the intussusception was diagnosed within 48 hours in most of the cases.[11] Okuyama et al concluded that barium enema reduction was safe and effective regardless of the duration of the disease.[12] Also, in a study conducted in a tertiary referral center in Hong Kong, Wong et al found that a mean duration of symptoms of 2.3 days did not affect success rate of the reduction.[13] Yao et al conducted a study on 316 operated intussusception patients with failed nonoperative reduction. In that study, the median duration of symptoms in the overall patients, group with an unviable intestine, and group with a viable intestine was 23, 42, and 19 hours, respectively, and this result was significantly different.[14] Long duration of symptoms before presentation related to increase in the loss of intestinal viability. So, the duration of symptoms was not a contraindication for the nonoperative reduction, and some cases with a long symptom duration (minimum =1 hour and maximum =120 hours in success group) in our study had successful reduction. So, the presence of intestinal viability is an important risk factor associated with failed reduction. In this study, we found that duration of symptoms >72 hours before presentation was one of the predictors of failed nonoperative reduction.

None of the reviewed literature mentioned about the patient's weight as a risk factor for failed reduction, while most of the studies mentioned about the age of patients. Fallon et al[15] and Tota-Maharaj et al[16] found that an age <1 year was

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Table 2 Baseline characteristics (signs and investigations) of children with failed (n=76) and successful (n=94) nonsurgical reduction of intussusception

Characteristics	Failed, n (%)	Successful, n (%)	*P*-value
Signs			
Temperature (°C)[a]	37.51 (0.68)	37.12 (0.62)	<0.001
Palpable mass	55 (48.67)	58 (51.33)	0.191
Location			0.042
Right lower quadrant	8 (53.33)	7 (46.67)	
Right upper quadrant	35 (36.08)	62 (63.92)	
Left upper quadrant	16 (51.61)	15 (48.39)	
Left lower quadrant	15 (65.22)	8 (34.78)	
In rectum	0 (0)	0 (100)	
Investigations			
White blood cell count (mm^3)[b]	12,780 (9,400–17,100)	10,935 (8,885–14,850)	0.172
Neutrophils (%)[a]	56.00 (17.37)	56.81 (15.95)	0.757
Na (mmol/L)[a]	136.13 (4.52)	137.75 (3.61)	0.013
K (mmol/L)[b]	3.9 (3.5–4.3)	4.1 (3.6–4.4)	0.074
Cl (mmol/L)[a]	102.16 (5.69)	104.2 (4.91)	0.016
Total CO_2 (mmol/L)[a]	19.46 (3.24)	19.44 (3.90)	0.971
Plain abdominal X-ray (small bowel obstruction)	55 (51.40)	52 (48.60)	0.012
Ultrasound (poor prognosis sign)	35 (51.47)	33 (48.53)	0.330
Method of reduction			0.036
Hydrostatic	33 (55.93)	26 (44.07)	
Pneumatic	43 (38.74)	68 (61.26)	

Notes: [a]Presented as mean (standard deviation). [b]Presented as median (interquartile range).

significantly associated with failed reduction. In our study, we used the age for clustering the risk factors because the risk of pathologic leading point was higher in the children aged >3 years and might not be comparable. So, we used weight as a predictor and found that weight <12 kg was significantly associated with failed reduction. This result may be contributed to the small caliber of the small bowel of the small children. So, the intussusception was difficult to reduce.

Abdominal pain and vomiting are the two classic symptoms of intussusception. From the previous study, vomiting was found to be a symptom helpful in the diagnosis of intussusception but not a statistical significant predictor of failed reduction as found in our study.

Rectal bleeding and abdominal mass are the two classic signs of intussusception. He et al found that rectal bleeding was a predictor of failed reduction as in our study.[7] Palpable abdominal mass was also a significant factor associated with failed reduction in our study and in the study of Wong et al.[13] Regarding the location of the mass, He et al also found that the intussusception located on the left side of the abdomen was significantly associated with a lower success rate of reduction. Flaum et al found that ileocecal and ascending colon localization was associated with successful reduction.[17] In our study, a mass located on the left side of abdomen was significantly associated with failed reduction. Most cases of intussusception were of ileocolic type. The location of the mass represents the length of intussusception. The length of intussusception was not mentioned in the previous study as a predictor, but some studies on small bowel intussusception used the length of intussusception to differentiate the

Table 3 Multivariable risk ratio of prognostic indicators for failed reduction of intussusception clustered by an age of 3 years

Characteristics	Crude risk ratio (95% confidence interval)	*P*-value	Multivariable risk ratio (95% confidence interval)	*P*-value
Weight <12 kg	3.81 (2.43–5.98)	<0.001	1.48 (1.13–1.94)	0.004
Duration of symptoms >48 hours	1.24 (0.87–1.77)	0.224	1.26 (1.25–1.26)	<0.001
Vomiting	2.22 (1.42–3.48)	<0.001	1.63 (1.54–1.73)	<0.001
Rectal bleeding	2.53 (2.27–2.83)	<0.001	1.50 (1.20–1.89)	<0.001
Abdominal distension	2.02 (1.49–2.74)	<0.001	1.60 (1.18–2.17)	0.003
Temperature >37.8°C	2.10 (1.82–2.42)	<0.001	1.51 (1.47–1.55)	<0.001
Palpable mass	1.32 (1.09–1.60)	0.004	1.26 (1.24–1.28)	<0.001
Location (left over right side)	1.52 (1.48–1.55)	<0.001	1.48 (1.40–1.56)	<0.001
Ultrasound (poor prognosis sign)	1.21 (1.12–1.31)	<0.001	1.35 (1.29–1.42)	<0.001
Method of reduction (hydrostatic over pneumatic)	1.44 (1.11–1.88)	0.006	1.34 (1.04–1.71)	0.023

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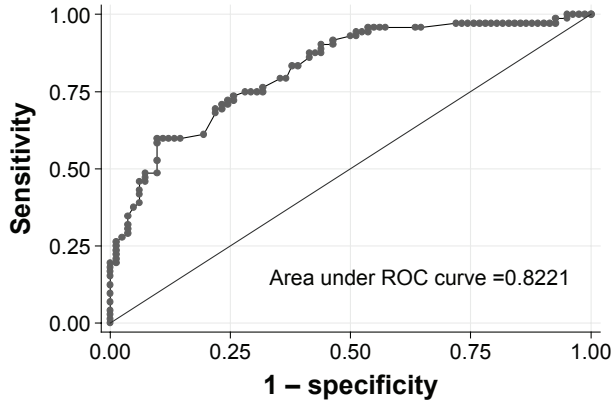

Figure 2 ROC curve of the model of prognostic indicators for failed reduction of intussusception predicted by the prognostic indicators (curved line) and a 50% chance prediction (diagonal line).
Abbreviation: ROC, receiver operating characteristic.

transient intussusception and to surgically manage small bowel intussusception. Actually, an intussusception of 2 cm diameter without clinical signs that could be spontaneously reduced is the transient intussusception.[1] Rajagopal et al studied about the transient and surgically managed small bowel intussusception and found that transient intussusception was associated with a shorter length of intussusception, smaller transverse diameter, thin walls, absence of the leading point, and visible peristalsis. The mean length of the transient intussusception in that study was 2.25 cm.[18]

In 2008, Ramachandan found that small bowel obstruction was one of the risk factors for failed reduction.[19] In our study, the plain abdominal X-ray showed that small bowel obstruction was significantly associated with failed reduction in univariable analysis but not in multivariable analysis. Therefore, we found that abdominal distension was associated with reduction failure.

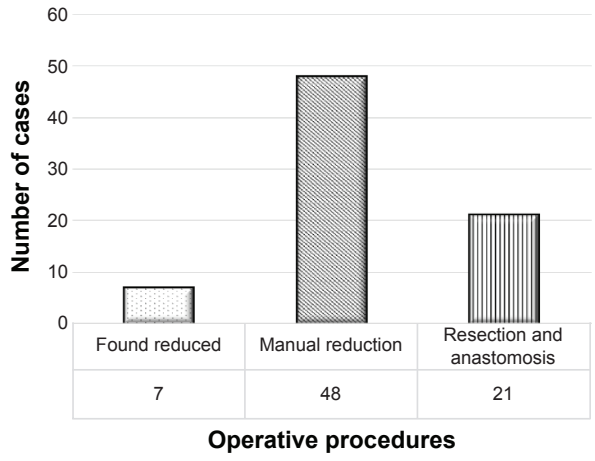

Figure 3 The operative procedures of the intussusception patients with failed nonoperative reduction (N=76).

Fever in the previous study was considered as a risk factor for bowel resection as reported by Fike et al.[20] However, a temperature >37.8°C was one of the predictors of failed reduction in our study. That might be a systemic response to intraabdominal infection and inflammation. The blood supply to intussusception might be compromised and associated with the lower success rate of reduction.

The poor prognosis signs on ultrasound scans were reported to be associated with the successful reduction in many studies. He et al also reported the presence of peritoneal fluid and trapped fluid in the intussusception as the predictors as found in our study.

In our previous series of intussusception, we studied about the method of reduction and found that the success rate of pneumatic reduction was 1.48 times more than hydrostatic reduction.[5] Sanchez et al found that the reduction under ultrasonography and fluoroscopy was equally effective.[21] Sadigh et al conducted a meta-analysis on air-versus-liquid enema of intussusception and found that air enema was superior to liquid enema with lower complication.[22] So, the method of reduction was considered to be one of the predictors in our study.

Among the 76 cases who were operated, we found reduction in only four cases. Those cases with reduction were reviewed based on the technique of reduction and the adequacy of the sedation. In 2010, Tota-Maharaj used sedation as one of the risk factors for failed reduction. The rest of the operative cases were operated with manual reduction or bowel resection depending on the viability of the intestine.

In our series, we found eight patients (4.7%) with recurrent intussusception. Three episodes of recurrent intussusception were found in one case, and two episodes in another. The nonoperative reduction was successful in seven cases, and manual reduction was done in failed case without pathologic leading point. The recurrence rate of intussusception was up to 20% with an average of 5% in the literature.[1] Gray et al presented a meta-analysis of the recurrence rate of nonoperative reduction. They found that the recurrence rates were 12.7% for contrast enema, 7.5% for ultrasound-guided noncontrast enema, and 8.5% for fluoroscopy-guided air enema.[23]

Bratton et al studied about hospital size and found that nonsurgical reduction was more likely to succeed in large hospitals with a larger caseload.[24] In contrast, in this study, we found that duration of symptoms was significantly associated with failed reduction. In our centers, we received the cases from the referral hospital with no pediatric surgeon. So, the duration of symptoms of cases in our study was longer than the previous studies. The median duration of symptoms before

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presentation in our study was 34.8 hours which was also mentioned in our first series. We also performed nonsurgical reduction safely if the contraindications were not present.

Guo et al reviewed a large series of studies on intussusception which used air enema for reduction.[25] They established a clinical criteria scoring system for intussusception by procedure used, duration of onset, age, stool characteristics, coexistent diarrhea, abdominal distension, and dehydration to predict the success rate. No other study proposed about the prediction factors for the successful intussusception reduction. In this study, we identified the significant risk factors associated with failed reduction. The information about prognosis of the nonoperative reduction could be provided to the referral hospital and parents. However, this was a retrospective study which was a limitation.

Conclusion

Many factors that can significantly predict the failure of nonsurgical reduction were found which included bodyweight <12 kg, symptoms duration >3 days, vomiting, rectal bleeding, abdominal distension, temperature >37.8°C, palpable abdominal mass, location of mass on the left side, poor prognostic signs on ultrasound scans, and method of reduction (hydrostatic over pneumatic). The contraindications for the nonsurgical reduction were peritonitis, free air in abdominal radiography, and nonresponsive shock. This study aimed to identify the risk factors for failure reduction, and in the next study, we will investigate the scoring system for the prediction of the failure of the reduction of intussusception.

Disclosure

The authors report no conflicts of interest in this work.

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Appendix D

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ORIGINAL RESEARCH

Clinical prediction rules for failed nonoperative reduction of intussusception

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Purpose: The nonoperative reduction of intussusception in children can be performed safely if there are no contraindications. Many risk factors associated with failed reduction were defined. The aim of this study was to develop a scoring system for predicting the failure of nonoperative reduction using various determinants.

Patients and methods: The data were collected from Chiang Mai University Hospital and Siriraj Hospital from January 2006 to December 2012. Inclusion criteria consisted of patients with intussusception aged 0–15 years with no contraindications for nonoperative reduction. The clinical prediction rules were developed using significant risk factors from the multivariable analysis.

Results: A total of 170 patients with intussusception were included in the study. In the final analysis model, 154 patients were used for identifying the significant risk factors of failure of reduction. Ten factors clustering by the age of 3 years were identified and used for developing the clinical prediction rules, and the factors were as follows: body weight <12 kg (relative risk [RR] =1.48, P=0.004), duration of symptoms >48 hours (RR =1.26, P<0.001), vomiting (RR =1.63, P<0.001), rectal bleeding (RR =1.50, P<0.001), abdominal distension (RR =1.60, P=0.003), temperature >37.8°C (RR =1.51, P<0.001), palpable mass (RR =1.26, P<0.001), location of mass (left over right side RR =1.48, P<0.001), ultrasound showed poor prognostic signs (RR =1.35, P<0.001), and the method of reduction (hydrostatic over pneumatic, RR =1.34, P=0.023). Prediction scores ranged from 0 to 16. A high-risk group (scores 12–16) predicted a greater chance of reduction failure (likelihood ratio of positive [LR+] =18.22, P<0.001). A low-risk group (score 0–11) predicted a lower chance of reduction failure (LR+ =0.79, P<0.001). The performance of the scoring model was 80.68% (area under the receiver operating characteristic curve).

Conclusion: This scoring guideline was used to predict the results of nonoperative reduction and forecast the prognosis of the failed reduction. The usefulness of these prediction scores is for informing the parents before the reduction. This scoring system can be used as a guide to promote the possible referral of the cases to tertiary centers with facilities for nonoperative reduction if possible.

Keywords: intussusception, nonoperative reduction, failure rate, clinical prediction rules

Introduction

Intussusception was a common cause of bowel obstruction and lower gastrointestinal bleeding in infants and children with an incidence of one to four in 2000.[1] The invagination of one part of the intestine into another distal part causes intussusception. Two of the most common symptoms are vomiting and colicky abdominal pain. In addition, the two most common signs are an abdominal mass and rectal bleeding.[1] The diagnosis of intussusception can be determined by ultrasound with 100% accuracy by an experienced

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Dovepress
http://dx.doi.org/10.2147/TCRM.S115253

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examiner and according to the clinical case definition for the diagnosis of acute intussusception proposed by the Brighton Collaboration Intussusception Working Group.[2]

Currently, treatment modalities for intussusception comprise nonsurgical and surgical treatment. The attempt of nonsurgical treatment is performed if no contraindications are present, which include signs of perforation (peritonitis, pneumoperitoneum in a plain abdominal X-ray) and a hemodynamically unstable patient in spite of adequate resuscitation. Surgical treatment is performed when nonsurgical treatment is contraindicated or has failed. The nonsurgical reduction procedure can be performed by hydrostatic or pneumatic pressure enema under ultrasound or fluoroscopy.

The diagnosis and treatment methods vary around the world depending on resources and equipment. In 2013, Jiang et al[3] reviewed global intussusception. The findings indicated that 95%–100% of the cases were diagnosed by a radiographic study (air contrast enema, ultrasound, or computed tomography) in all the World Health Organization regions except Africa where 65% of cases were diagnosed by clinical findings or surgery. The global incidence of treatment with air or barium enema accounted for 66%. In Africa and Central and South America, the primary treatment was surgery. In recent reports of some areas, surgery was still the primary treatment.[4]

The reported success of nonsurgical reduction in the literature ranged from 46% to 94%.[5] Risk factors associated with failed reduction were studied in some series. In 2014, He et al[6] reported that initial intussusception was located in the descending colon/rectum with the presence of peritoneal fluid, trapped fluid in the intussusception, and bloody stools as the factors. In 2013, Fallon et al[7] described the predictors of abdominal symptoms >2 days, age <1 year, and multiple ultrasound findings. Our earlier series studied the prognosis indicators for failed reduction and found that body weight <12 kg, duration of symptoms >3 days, vomiting, rectal bleeding, abdominal distension, temperature >37.8°C, palpable abdominal mass, location of mass on the left side, ultrasound showing poor prognostic signs, and the method of reduction (hydrostatic over pneumatic) were the factors.[8]

Many factors seem to influence successful or failed reduction. In this study, we aimed to develop a scoring system for predicting the failure of nonsurgical reduction using various determinants that were found in the earlier studies.

Patients and methods

This retrospective cohort study was approved by the ethics committees of Chiang Mai University (CMU) Hospital and Siriraj (SI) Hospital. Due to the retrospective nature of this study, both committees waived the need for patient consent. This study was the third study in cluster of study series regarding intussusception. The first study reported comparative results of the success rates of hydrostatic and pneumatic reduction.[9] The second study reported the prognostic indicators of failed operative reduction.[8] This was the third study that used ten prognostic factors for failed nonsurgical reduction derived from the second study.

Patients

This was a two institution review. The data were collected from patient charts and electronic medical records of the patients with intussusception (ICD-10 code K56.1) in CMU and SI. The study period was between January 2006 and December 2012. We included the patients who were diagnosed with intussusception from the age of 0 year to 15 years who received nonsurgical reduction as an initial treatment. We excluded patients who had contraindications for nonsurgical reduction at presentation. Absolute contraindications were peritonitis, pneumoperitoneum in abdominal X-ray, and hemodynamic instability. The method of nonsurgical reduction in CMU was all pneumatic reduction under fluoroscopy, whereas the main method of reduction in SI was hydrostatic reduction under fluoroscopy by radiologist. Thus, the method of reduction could be used as one of the predictors.

Predictive variables

The chart and electronic database reviews collected the data of following ten significant factors: body weight, duration of symptoms, vomiting, rectal bleeding, abdominal distension, temperature, palpable abdominal mass, location of mass, ultrasound showed poor prognostic signs, and the method of reduction. The demographic data such as age and sex were also collected. Poor prognostic signs by ultrasound were a thick peripheral hypoechoic rim, free intraperitoneum fluid, fluid trapped within the intussusception, enlarged lymph node in intussusception, pathologic leading point, and the absence of blood flow in the intussusception, and were counted if one of these signs mentioned was present.

Outcome variables

The results of the nonsurgical reductions were collected. The patients were divided into two groups: a successful reduction group and a failed reduction group.

Statistical analysis

The statistical analysis was performed by using commercial statistical software (STATA 11.0; StataCorp LP, College Station, TX, USA). The data were presented in count and

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percentage. The univariable comparative statistics were performed by Fisher's exact test for categorical data and by Student's *t*-test or Mann–Whitney *U*-test for continuous data depending on data distribution. Generalized linear model for exponential risk regression clustering by the age of 3 years (due to the risk for pathologic leading point) was used for multivariable analysis.

Ten significant risk factors were used for the clinical prediction model for failed reduction of intussusception derivation. Numerical factors such as body weight, duration of symptoms, and temperature were divided into two groups. The cutoff points were determined from the values that yielded all statistically significant regression coefficients and the highest area under the receiver operating characteristic (ROC) curve of the logistic regression model.

The regression coefficients of each factor were transformed into item scores. All item scores were added together for a total score. The total scores were used as a predictor for failed nonsurgical reduction of intussusception. The risk level was to categorize total scores into a low-risk group and a high-risk group. The cutoff points for the total scores were determined from the values that yielded the lowest likelihood ratio of positive for failed reduction in the low-risk group and highest likelihood ratio of positive for failed reduction in the high-risk group. The statistical significance level was set as two tailed with a *P*-value of <0.05.

Table 1 Characteristics of children with intussusception with failed (n=76) and successful (n=94) nonsurgical reduction

Characteristics	Failed, n (%)	Successful, n (%)	*P*-value
Demography			
Weight (kg)[a]	8.61 (1.98)	10.15 (3.90)	
Weight ≤12 kg	73 (49.66)	74 (50.34)	0.001
Weight >12 kg	3 (13.04)	20 (86.96)	
Symptoms			
Duration of symptoms (hours)[b]	24 (24)	24 (30)	
Duration ≤48 hours	60 (42.86)	80 (57.14)	0.318
Duration >48 hours	16 (53.33)	14 (46.67)	
Vomiting	71 (48.30)	76 (51.70)	0.023
Rectal bleeding	65 (54.62)	54 (45.38)	<0.001
Abdominal distension	48 (61.54)	30 (38.46)	<0.001
Signs			
Temperature (°C)[a]	37.51 (0.68)	37.12 (0.62)	
Temperature ≤37.8°C	48 (36.09)	85 (63.91)	<0.001
Temperature >37.8°C	28 (75.68)	9 (24.32)	
Palpable mass	55 (48.67)	58 (51.33)	0.191
Location			
Right side	43 (38.39)	69 (61.61)	0.020
Left side	32 (58.18)	23 (41.82)	
Investigations			
Ultrasound (poor prognosis sign)	35 (51.47)	33 (48.53)	0.330
Method of reduction			
Hydrostatic	33 (55.93)	26 (44.07)	0.036
Pneumatic	43 (38.74)	68 (61.26)	

Notes: [a]Mean (standard deviation). [b]Median (interquartile range).

Results

A total of 190 episodes of intussusception were collected from two institutions. Primary surgery at first visit was performed in 20 patients due to contraindications for nonsurgical reduction. According to the retrospective study, some of the missing data were found in 16 records. A total of 154 episodes of intussusception were collected for final prediction model analysis. The median age of the included patients was 9 months (maximum 124 months). There were 114 boys (67%) and 56 girls (33%). The comparative characteristics of 170 patients with intussusception who had successful reductions and failed nonsurgical reductions are shown in Table 1. The mean weight was significantly lower in the failed group (mean 8.61±1.98 in the failed group vs mean 10.15±3.90 in the successful group, $P=0.002$). Rectal bleeding and abdominal distension were found more in the failed group (54.62% vs 45.38%, $P<0.001$, and 61.54% vs 38.46%, $P<0.001$ respectively). The mean body temperature was slightly higher in the failed group (mean 37.51±0.68 in the failed group vs mean 37.12±0.62 in the successful group, $P<0.001$). Masses were located more on the left side in the failed group (58.18% vs 41.82%, $P=0.020$). Hydrostatic reduction was also found more frequently in the failed group (55.93% vs 44.07%, $P=0.036$). The median duration of symptoms, palpable abdominal mass, and ultrasound findings with poor prognostic signs were not significantly different in univariable analysis.

Ten prognostic factors were identified from the earlier studies with statistical differences between the failed and successful reduction groups in multivariable analysis by exponential risk regression, which are shown in Table 2. Risk scoring assignment was performed to forecast the possibility of a failed nonsurgical reduction of intussusception. The regression coefficients were transformed to transform coefficients by dividing with the smallest coefficient in the model which was 0.23 and then rounded up to the nearest integer to be an assigned score. The Item Scoring Scheme is shown in Table 3. The total scores ranged from 0 to 16.

After using the ten parameters that were transformed into a score, the ROC curve of the failed nonoperative reduction of intussusceptions predicted by risk scoring scheme was performed. The area under the ROC curve that determined

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Table 2 Regression coefficient, RR, and 95% CI of selected risk indicators for failed reduction of intussusceptions derived from generalized linear model

Risk indicators	Coefficients	RR	95% CI of RR	*P*-value
Weight ≤12 kg	0.39	1.48	1.13–1.94	0.004
Duration of symptoms >48 hours	0.23	1.26	1.25–1.26	<0.001
Vomiting	0.49	1.63	1.54–1.73	<0.001
Rectal bleeding	0.41	1.50	1.20–1.89	<0.001
Abdominal distension	0.47	1.60	1.18–2.17	0.003
Temperature >37.8°C	0.41	1.51	1.47–1.55	<0.001
Palpable mass	0.23	1.26	1.24–1.28	<0.001
Location (left over right side)	0.39	1.48	1.40–1.56	<0.001
Ultrasound (poor prognosis sign)	0.30	1.35	1.29–1.42	<0.001
Method of reduction (hydrostatic over pneumatic)	0.29	1.34	1.04–1.71	0.023

Abbreviation: RR, relative risk.

Table 3 Item scoring scheme for predictors for failure reduction of intussusception derived from coefficients of selected indicators

Risk indicators	Coefficients	Transformed coefficients	Assigned score
Weight			
≤12 kg	0.39	1.70	2
>12 kg	–	–	0
Duration of symptoms			
≤48 hours	–	–	0
>48 hours	0.23	1	1
Vomiting			
No	–	–	0
Yes	0.49	2.13	2
Rectal bleeding			
No	–	–	0
Yes	0.41	1.78	2
Abdominal distension			
No	–	–	0
Yes	0.47	2.04	2
Temperature >37.8°C			
No	–	–	0
Yes	0.41	1.78	2
Palpable mass			
No	–	–	0
Yes	0.23	1	1
Location			
Right	–	–	0
Left	0.39	1.70	2
Ultrasound (poor prognosis sign)			
No	–	–	0
Yes	0.30	1.30	1
Method of reduction			
Pneumatic	–	–	0
Hydrostatic	0.29	1.26	1

the prediction ability of the score model was 80.68% as shown in Figure 1.

The total scores were categorized into a low-risk group (scores 0–11) and a high-risk group (scores 12–16) as shown in Table 4. The majority of the failed reduction patients were in the high-risk group (94.1%). The majority of the successful reduction patients were in the low-risk group (59.1%). The likelihood ratio of positive showed the probability of failed reduction in each group. Patients with intussusception in the low-risk group were 0.79 times more likely to have a failed nonsurgical reduction. However, the patients in the high-risk group were 18.22 times more likely to have a failed nonsurgical reduction. Figure 2 shows a relationship between the proportion of failed reductions with the total scores. The higher the score, the increased proportion of failed reductions was shown which corresponded to the estimated risk from logistic estimation. The goodness of fit by Hosmer–Lemeshow chi-square test of this model was performed for assessing the fit of the model. There was no evidence of lack of fit (P=0.876).

Discussion

Intussusception is a common disease in infants and children around the world. The method of diagnosis and management of intussusception have developed over time. Investigations for the diagnosis of intussusception have gradually changed from intraoperative diagnosis and contrast enema to ultrasonography. The management also developed from primary surgery to nonsurgical reduction if there were no contraindications. Nonsurgical reduction has also varied in the techniques. The development of hydrostatic and pneumatic reduction techniques under radiologic guidance

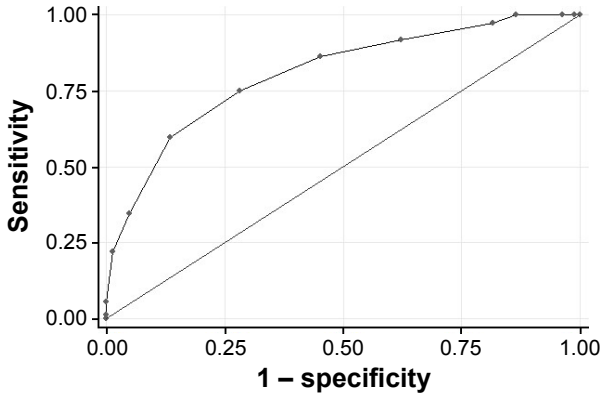

Figure 1 The ROC curve of failure nonoperative reduction of intussusceptions predicted by risk scoring scheme (curved line) and a 50% chance prediction (diagonal line).
Notes: Area under the ROC curve =0.8068; 95% Confidence Interval = 0.7390–0.8762.
Abbreviation: ROC, receiver operating characteristic.

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Table 4 Distribution of risk of failed nonoperative reduction of intussusceptions, LR+ and 95% CI of LR+

Risk level	Failed, n (%)	Successful, n (%)	LR+	95%CI of LR+	*P*-value
Low (score ≤11)	56 (40.9)	81 (59.1)	0.79	0.69–0.89	<0.001
High (score >11)	16 (94.1)	1 (5.9)	18.22	2.48–134.02	<0.001

Abbreviation: LR+, likelihood ratio of positive.

(ultrasonography or fluoroscopy) has still been reported.[10–13] The decision for the method of diagnosis and treatment was dependent on patient characteristics, experience of patient care team (surgeons, radiologists, and pediatricians), facilities, and equipment.

In 2013, Jiang et al[3] collected the published data of intussusception in seven geographic regions of the world. He reported that the diagnosis of intussusception was mostly found by ultrasound in Central and South America, contrast enema in Eastern Mediterranean, and surgery in Africa. For the management, primary treatment was air or barium enema except in Africa and Central and South America where surgery was the primary treatment.

In our study, nonsurgical reduction was attempted if there were no contraindications with a success rate of 55.3%. We studied the prognostic indicators for failed reduction and found ten parameters in our earlier study.[8] There were a few earlier reports about predictors in the literature. In 2016, Ntoulia et al[14] reported that the ultrasound findings of a distal mass and observation of the dissecting sign were the predictors for failed reduction. In 2015, Wong et al[15] found a palpable abdominal mass to be a risk factor. In 2014, He et al[6] found that the presence of bloody stool, free peritoneal fluid, trapped fluid in the intussusception, and location in the left side of the abdomen were associated with a lower success rate. Our study found that the predictors included the clinical signs and symptoms along with the ultrasound findings and mode of reduction.

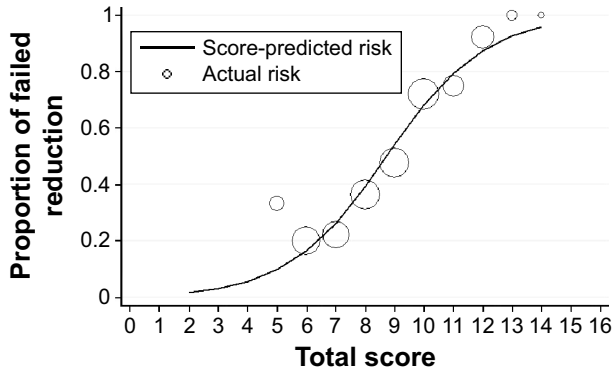

Figure 2 Score-predicted risk (line) and actual risk (circles) of failed nonsurgical reduction of intussusception for each total score.

From the earlier reviews, there were some scoring systems. In 1986, Guo et al[16] reported a large series of intussusception treated with air pressure enema. In that study, he proposed a clinical criteria scoring system as a guide in the determination of initial treatment. The parameters in that scoring system were the clinical signs and symptoms. In 2011, Weihmiller et al[17] set up the clinical criteria for the diagnosis of intussusception with a decision tree. His criteria, however, did not indicate a clinical prediction for failed reduction. In our study, we set up clinical prediction rules for predicting the failure of nonsurgical reduction of intussusception. We used the parameters from demography (body weight), symptoms (duration of symptoms, vomiting, rectal bleeding, and abdominal distension), signs (body temperature, palpable mass, and location of the mass), sonographic findings, and the method of reduction to calculate the scores.

The prediction of the nonsurgical reduction results might help the physician to communicate with the parents about the importance of attempting a nonsurgical reduction and prognosis of the patient. In some areas with no facilities for reduction, surgery was the treatment. The prediction scores may be used to facilitate the referral of cases to the center in which nonsurgical reduction could be performed. However, this study was a retrospective study that was one of our limitations. The validation of this prediction score should be performed before its actual use.

Conclusion

These scoring guidelines were used to predict the results of nonoperative reduction and forecast the prognosis of the failed reduction. The usefulness of these prediction scores was to inform the parents before the reduction. These scores can be used as a guide to promote the referral of the cases to tertiary centers with facilities for nonoperative reduction if possible. Nevertheless, contraindications preventing nonoperative reduction still remain such as peritonitis, free air in abdominal X-ray, and nonresponsive shock. Validation for these scores is planned for the next study.

Disclosure

The authors report no conflicts of interest in this work.

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