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Etiology of Hematochezia in Children: Clinical Analysis of 1122 Hospitalized Cases in China

Li J[1,2], Zhang D[1,2], Wang Y[1,2] and Zhan X[1,2*]

[1]Department of Gastroenterology, Children's Hospital of Chongqing Medical University; Chongqing, China

[2]Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, China

***Corresponding author:**

Xue Zhan,

Department of Gastroenterology, Children's Hospital of Chongqing Medical University; Chongqing, 400014, China, Tel:023-63742502;

E-mail: zhanxue@hotmail.com

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Keywords:

Children; Hematochezia; Gastrointestinal; Bleeding; Etiology

Abbreviations:

BUN: Blood urea nitrogen; Cr: Creatinine; EGV: Esophageal and gastric varices; HSP: Henoch-Schoenlein purpura; IQR: Interquartile Range; LGIB: Lower gastrointestinal bleeding; OGIB: Obscure gastrointestinal bleeding; PU: Peptic ulcer; UGIB: Upper gastrointestinal bleeding

1. Abstract

1.1. Objectives: To investigate the etiology and clinical characteristics of hematochezia in children.

1.2. Methods: 1122 children older than 28 days admitted to Children's Hospital of Chongqing Medical University from October 1, 2017 to October 1, 2018 with a chief complaint of hematochezia were analyzed retrospectively.

1.3. Results: Lower gastrointestinal bleeding (70.7%) was the most common bleeding site of hematochezia, followed by upper gastrointestinal bleeding (8.0%). In upper gastrointestinal bleeding, the most common etiology was peptic ulcer and esophageal and gastric varice, while in lower gastrointestinal bleeding was intussusception and intestinal polyp. The top 10 etiologies were intussusception (39.8%), Henoch-Schoenlein purpura (14.3%), enteritis (10.3%), intestinal polyp (8.4%), perianal diseases (6.9%), digestive tract malformation (5.2%), peptic ulcer (4.1%), hematological diseases (3.8%), esophageal and gastric varice (2.4%), and obscure gastrointestinal bleeding (1.4%) respectively. Etiology varied by age groups: the most common etiology in infant and toddler was intussusception; while in older children was HSP. There was difference in major accompanying symptoms and laboratory results among etiologies, whereas no difference in blood urea nitrogen to creatinine ratio between upper gastrointestinal bleeding and lower gastrointestinal bleeding.

1.4. Conclusions: Except for lower gastrointestinal bleeding, upper gastrointestinal bleeding and systemic diseases should be considered as the cause of hematochezia in children. The top 3 etiologies were intussusception, HSP, enteritis. And etiology varied by age groups: the most common etiology in infant and toddler was intussusception; while in older children was HSP. The blood urea nitrogen to creatinine ratio could not differentiate upper gastrointestinal bleeding from lower gastrointestinal bleeding.

2. Introduction

Hematochezia, defined as the bright red or maroon blood from the rectum (with red blood noted either on or within the stool, on the toilet paper or in the toilet bowl) [1], is a common complaint in children. Hematochezia is predominantly of a chronic course with relatively stable vital sign, however it can be life-threatening with an acute massive bleeding [2]. Epidemiological studies of hematochezia in children are very limited, and almost all only indicated the incidence of gastrointestinal bleeding, especially lower gastrointestinal bleeding (LGIB). For example, in the United States, the incidence of LGIB in 2005 was 20.5-27/100,000 [3]. From 2006 to 2011, the incidence of gastrointestinal bleeding in children increased from 82.18/100,000 to 93.93/100,000 [4], mainly due to the increased incidence of LGIB,

which was consistent with a study from Spain [5]. Moreover, the lowest incidence of LGIB is in the Netherlands (8.9/100,000) [6] and the highest in China (50-150/100,000) [7]. However, the above epidemiological data are not fully representative, even far below the actual incidence of hematochezia. Since, except for LGIB, upper gastrointestinal bleeding (UGIB), unclassified gastrointestinal bleeding can also cause hematochezia, making the diagnosis a challenging one. With the development of diagnostic modalities such as capsule endoscopy, CT enterography, and Technetium 99m pertechnetate scan, the diagnosis rate has been greatly improved in recent years. Some etiologies previously defined as "obscure gastrointestinal bleeding (OGIB)" have been gradually identified8. Hitherto, several retrospective studies focusing on the etiology of hematochezia in children have been carried out in

China, but no consensus on the etiological distribution has been arrived due to small sample size, and exclusion of perianal diseases and systemic diseases. To further explore the etiological distribution of hematochezia in children in China, we retrospectively analyzed the cases of children with hematochezia admitted in our hospital from 2017 to 2018, so as to assist in diagnosis, treatment, and improve prognosis.

3. Material and Methods

Children admitted to the Children's Hospital Affiliated to Chongqing Medical University from October 1, 2017 to October 1, 2018, with hematochezia as chief complaint were selected for our research.

3.1. Inclusion Criteria

1. The chief complaint was hematochezia (with red blood noted either on or within the stool, on the toilet paper or in the toilet bowl).
2. Hospitalized children.

3.2. Exclusion Criteria

1. Neonates (age < 28 days old).
2. Pseudo-hematochezia caused by excessive intake of animal viscera, spinach, blueberry or taking iron or traditional Chinese medicine.
3. Bleeding originated from nasal or oral cavity, or swallowing syndrome.
4. Diagnosis with OGIB without results of esophago-gastro-duodenoscopy, colonoscopy and radiologic evaluation.

3.3. Data Collection

Demographic data including age, sex and information such as accompanying symptom, initial laboratory test result, radiologic examination and endoscopy findings done on patients' first visit in the emergency room were collected.

3.4. Grouping

Case samples were classified into five groups according to age: Infant (0-1-year-old), toddler (1-3 years old), pre-school age (3-6 years old), school age (6-12 years old) and adolescent (12-18 years old). Based on the site of bleeding, the patients were classified into four groups: UGIB, LGIB, systemic diseases and OGIB. The bleeding site of UGIB is the part between esophagus and the Treitz ligament, while LGIB is the part between the Treitz ligament and the anus. Systemic diseases refer to diseases originated outside of digestive system, like hematological diseases. OGIB refers to etiology remains unclear after radiologic evaluation, esophago-gastro-duodenoscopy, and colonoscopy.

3.5. Statistics Methods

SPSS 21.0 software was used for data analysis. The enumerated data was presented by using ratios and percentages. Chi-square test or continuous correction Chi-square or Fisher exact test was used for comparison between groups. As for measurement data; the normal distribution was described by mean and standard deviation whereas t-test or variance analysis was used for comparison among groups; while median and Interquartile Range (IQR) were used for description of skewed distribution, rank sum test was used for comparison between groups. $P<0.05$ was taken as statistically significant. In order to reduce type I errors, Bonferroni correction was used to adjust for multiple comparisons.

4. Results

1122 children met the inclusion criteria and were recruited. Median age was 22 months old (IQR, 70.3 months). Out of 1122 cases recruited, 90 (8.0%) cases were diagnosed with UGIB, 793 (70.7%) with LGIB, 223 (19.9%) with systemic diseases, and 16 (1.4%) with OGIB (Table 1). The top 10 etiologies were intussusception (447 cases, 39.8%), Henoch-Schoenlein purpura (HSP) (160 cases, 14.3%), enteritis (115 cases, 10.3%), intestinal polyp (94 cases, 8.4%), perianal diseases (77 cases, 6.9%), digestive tract malformation (58 cases, 5.2%), peptic ulcer (PU) (46 cases, 4.1%),

hematological diseases (43 cases, 3.8%), esophageal and gastric varice (EGV) (27 cases, 2.4%), and OGIB (16 cases, 1.4%) respectively. In UGIB, PU, EGV and digestive tract malformation were the most common etiologies, whereas in LGIB, intussusception, intestinal polyp, and enteritis were more prevalent.

Infants, accounted for 39.6% (444/1122), making it largest age group admitted for hematochezia, followed by school age, toddler, preschool age and adolescent group. There was significant difference in the etiological composition of hematochezia among age groups (χ^2=794.835, $P<0.001$). The constituent ratio of intussusception in infant group (74.5%) was the highest among all the groups, and the constituent ratio of intestinal polyp in pre-school age group (22.9%) was higher than other groups, but not prominently different from toddler group (13.8%). However, the composition of PU (19.2%) in adolescent group is notably higher than others (Table 2). The top 3 etiologies in each age group were as followed: intussusception, en-

teritis, digestive tract malformation in infant group; intussusception, intestinal polyp, enteritis in toddler group; HSP, intestinal polyp, perianal diseases in pre-school group; HSP, perianal

diseases, intestinal polyp in school age group; HSP, PU, hematological diseases in adolescent group.

The sex ratio was 1.98:1 (745 and 377 for male and female respectively). There was no significant difference in the etiologies between genders (χ^2=15.536, P=0.077).

The top 10 accompanying symptoms were vomiting (50.3%), abdominal pain (29.1%), fever (19.8%), hematemesis (19.4%), rash (19.0%), diarrhea (13.1%), pallor (7.7%), constipation (4.5%), dizziness (4.3%) and anal prolapse (2.2%). For each accompanying symptom, significant difference was found among etiologies. The hematemesis rates of PU, EGV and intussusception, vomiting rate of intussusception, diarrhea rate of enteritis, abdominal pain and rash rate of HSP, constipation rate of perianal disease and intestinal polyp were all significantly higher (Table 3).

Laboratory tests were found to be statistically significant in relation to different etiologies. White blood cell count of HSP and intussusception, neutrophil ratio and D-dimer of HSP, and eosinophil count of enteritis all significantly increased. While platelet counts of hematological diseases and EGV significantly reduced. The mean values of hemoglobin of digestive tract malformation, PU and EGV, all below 90 g/L, were evidently lower than other etiologies (Table 4).

There was statistical significant difference in blood urea nitrogen (BUN) to creatinine(Cr) ratio among hemorrhagic sites (χ^2=17.884, P<0.001), but no difference between UGIB and LGIB (χ^2=70.128, P=0.310). The area under the ROC curve was 0.565, 95% confidence interval was 0.499-0.630, P=0.045. Using BUN/Cr=31.5 as the critical value, significant difference was found in the incidence of BUN/Cr ratio≥31.5 among hemorrhagic sites (χ^2=13.431, P=0.004), but no difference between UGIB and LGIB by the pairwise comparison (Table 5).

Table 1: The etiology of hematochezia in 1122 children [n(%)]

Hemorrhage site	**Etiology**		**n(%)**
UGIB			**90(8.0)**
	Gastritis		6(0.6)
		Acute gastric mucosal lesion	3(0.3)
		Acute attack of chronic gastritis	3(0.3)
	PU		46(4.1)
		Gastric ulcer	13(1.2)
		Duodenal ulcer	33(2.9)
	EGV		27(2.5)
		Cavernous transformation of portal vein	14(1.2)
		Cholestatic cirrhosis	3(0.3)
		Congenital hepatic fibrosis	2(0.2)
		Hepatocellular carcinoma	2(0.2)
		Hepatoblastoma	1(0.1)
		Cirrhosis of unknown origin	5(0.5)
	Digestive tract malformation		9(0.8)
		Hiatus hernia	6(0.5)
		Congenital Hypertrophic Pyloric Stenosis	1(0.1)
		Annular pancreas	1(0.1)
		Prepyloric membrane	1(0.1)
	Burkitt lymphoma of the stomach		1(0.1)
	Foreign body in digestive tract		1(0.1)
LGIB			**793(70.7)**
	Intussusception		447(39.8)
	Intestinal polyps		94(8.4)
	Enteritis		115(10.3)
		Food protein-induced enteritis	46(4.1)
		Infectious enteritis	54(4.8)
		Intestinal tuberculosis	1(0.1)
		Appendicitis	1(0.1)
		Necrotizing enterocolitis	2(0.2)
		Inflammatory bowel disease	3(0.3)

		Colitis	6(0.5)
		Eosinophilic gastroenteritis	2(0.2)
	Digestive tract malformation		49(4.4)
		Meckel's diverticulum	46(4.1)
		Congenital intestinal malrotation	2(0.2)
		Congenital multiple stricture of descending colon	1(0.1)
	Vascular malformation		5(0.5)
	Inguinal hernia		2(0.2)
	Perianal diseases		77(6.9)
		External hemorrhoid	30(2.7)
		Anal fissure	18(1.6)
		Anal Sinusitis	9(0.8)
		Two or three perianal diseases above	20(1.8)
	Anorectal trauma		4(0.4)
Systemic diseases			**223(19.9)**
	HSP		160(14.3)
	Hematological diseases		43(3.8)
		Primary immune thrombocytopenia	21(1.9)
		Leukemia	7(0.6)
		Hemophilia	2(0.2)
		Aplastic anemia	4(0.4)
		Hemolytic anemia	3(0.3)
		Coagulopathy	4(0.4)
		Myelodysplastic syndrome	1(0.1)
		Graft-versus-host disease	1(0.1)
	Immune system diseases		12(1.1)
		Systemic lupus erythematosus	1(0.1)
		Kawasaki disease	1(0.1)
		Wiskott Aldrich syndrome	10(0.9)
	Hepatopathy		3(0.3)
	Nephrosis		3(0.3)
	Toxicosis		2(0.2)
OGIB			**16(1.4)**

Table 2: The etiology of hematochezia in children among different age groups [n(%)]

Etiology	**Age group**						
	Infant	**Toddler**	**Pre-School age**	**School age**	**Adolescence**	**Total**	**P**
Intussusception	331(74.5)[a]	94(43.3)[b]	16(10.5)[c]	3(1.3)[d]	3(4.1)[cd]	447(39.8)	<0.001
HSP	1(0.2)[a]	4(1.8)[a]	38(24.8)[b]	89(37.9)[b]	28(38.4)[b]	160(14.3)	<0.001
Enteritis	71(16.0)[a]	21(9.7)[ab]	8(5.2)[b]	12(5.1)[b]	3(4.1)[ab]	115(10.2)	<0.001
Intestinal polyp	1(0.2)[a]	30(13.8)[bc]	35(22.9)[c]	26(11.1)[b]	2(2.7)[ab]	94(8.4)	<0.001
Perianal diseases	2(0.5)[a]	18(8.3)[b]	20(13.1)[b]	34(14.5)[b]	3(4.1)[b]	77(6.9)	<0.001
Digestive tract malformation	13(2.9)[a]	17(7.8)[b]	10(6.5)[ab]	14(6.0)[ab]	4(5.5)[ab]	58(5.2)	<0.001
PU	2(0.5)[a]	12(5.5)[b]	3(2.0)[ab]	15(6.4)[b]	14(19.2)[c]	46(4.1)	<0.001
Hematological diseases	10(2.3)[a]	9(4.1)[ab]	9(5.9)[ab]	8(3.4)[ab]	7(9.6)[b]	43(3.8)	<0.001
EGV	1(0.2)[a]	1(0.5)[ab]	7(4.6)[bc]	15(6.4)[c]	3(4.1)[bc]	27(2.4)	<0.001
OGIB	1(0.2)[a]	2(0.9)[ab]	4(2.6)[ab]	7(3.0)[b]	2(2.7)[ab]	16(1.4)	<0.001
Others	11(2.5)[a]	9(4.1)[a]	3(2.0)[a]	12(5.1)a	4(5.5)[a]	39(3.5)	<0.001
Total	444(100.0)	217(100.0)	153(100.0)	235(100.0)	73(100.0)	1122(100.0)	

Note: For each etiology (row), the same superscript letter denotes no statistically significant difference between every two age groups. For example, there was significant difference in the intussusception rate between infant (a) and school age group (d), while no difference between school age (d) and adolescence (cd) because they had a same superscript letter (d).

Table 3: The main accompany symptoms among etiologies [n (%)].

Etilogy													
Accompany symptom	Intussus-ception	HSP	Enteritis	Intestinal polyp	Perianal diseases	Digestive tract malformation	PU	Hematolo-gical diseases	EGV	OGIB	Others	Total	P
Vomiting	396(88.6)^{a}	75(46.9)^{b}	30(26.1)^{c}	7(7.4)^{de}	1(1.3)^{e}	18(31.0)^{bc}	16(34.8)^{bc}	3(7.0)^{cde}	4(14.8)^{bcde}	4(25.0)^{bcd}	10(25.6)^{bcd}	564(50.3)	<0.001
Abdominal pain	35(7.8)^{a}	160(100.0)^{b}	16(13.9)^{ac}	19(20.2)^{cd}	18(23.4)^{cde}	21(36.2)^{de}	23(50.0)^{e}	9(20.9)^{acde}	14(51.9)^{de}	10(62.5)^{e}	6(15.4)^{acd}	331(29.5)	<0.001
Fever	123(27.5)^{ab}	6(3.8)^{c}	47(40.9)^{b}	7(7.4)^{cd}	3(3.9)^{cd}	10(17.2)^{abd}	6(13.0)^{acd}	5(11.6)^{acd}	6(22.2)^{abd}	2(12.5)^{abcd}	7(17.9)^{abcd}	222(19.8)	<0.001
Hematemesis	162(36.2)^{a}	18(11.3)^{bc}	0(0.0)^{d}	0(0.0)^{de}	0(0.0)^{cde}	6(10.3)^{bce}	16(34.8)^{af}	2(4.7)^{bcde}	9(33.3)^{af}	1(6.3)^{bcde}	4(10.3)^{bce}	218(19.4)	<0.001
Rash	1(0.2)^{a}	158(98.8)^{b}	7(6.1)^{c}	1(1.1)^{ac}	1(1.3)^{ac}	0(0.0)^{ac}	0(0.0)^{ac}	10(23.3)^{c}	0(0.0)^{ac}	1(6.3)^{c}	34(87.2)^{d}	213(19.0)	<0.001
Diarrhea	27(6.0)^{a}	7(4.4)^{a}	91(79.1)^{b}	7(7.4)^{a}	4(5.2)^{a}	1(1.7)^{a}	3(6.5)^{a}	2(4.7)^{a}	0(0.0)^{a}	2(12.5)^{a}	3(7.7)^{a}	147(13.1)	<0.001
Pallor	2(0.4)^{a}	3(1.9)^{a}	2(1.7)^{a}	3(3.2)^{ab}	2(2.6)^{abc}	31(53.4)^{d}	22(47.8)^{de}	8(18.6)^{bce}	6(22.2)^{cde}	7(43.8)^{de}	0(0.0)^{abc}	86(7.7)	<0.001
Constipation	1(0.2)^{a}	2(1.3)^{ab}	0(0.0)^{ab}	18(19.1)^{cd}	25(32.5)^{d}	0(0.0)^{ab}	0(0.0)^{ab}	1(2.3)^{ab}	1(3.7)^{ab}	0(0.0)^{ab}	3(7.7)^{bc}	51(4.5)	<0.001
Dizziness	0(0.0)^{a}	3(1.9)^{ab}	1(0.9)^{ab}	1(1.1)^{ab}	1(1.3)^{ab}	12(20.7)^{c}	15(32.6)^{c}	3(7.0)^{bc}	4(14.8)^{bcde}	4(25.0)^{c}	4(10.30)^{bc}	48(4.3)	<0.001
Prolapse	0(0.0)^{a}	0(0.0)^{ab}	2(1.7)^{ab}	15(16.0)^{c}	5(6.5)^{bc}	0(0.0)^{abc}	0(0.0)^{abc}	1(2.3)^{abc}	0(0.0)^{abc}	0(0.0)^{abc}	2(5.1)^{bc}	25(2.2)	<0.001

Note: For each accompany symptom (row), the same superscript letter denotes no statistically significant difference between every two etiologies. For example, there was significant difference in vomiting rate between HSP (b) and intussusception (a), whereas no difference between HSP (b) and PU (bc) because they had a same superscript letter (b).

Table 4: The main laboratory index among the most common etiologies [median (IQR), mean±SD]

Etiology											
Laboratory index	**Intussu-sception**	**HSP**	**Enteritis**	**Intestinal polyp**	**Perianal diseases**	**Digestive tract malformation**	**PU**	**Hematol-ogical diseases**	**EGV**	**OGIB**	***P***
WBC (*10^9/L)	11.7(4.9)^{a}	12.2(10.6)^{a}	9.7(4.9)^{b}	7.2(3.1)^{b}	6.4(2.6)^{b}	7.7(4.0)^{b}	8.8(5.8)^{b}	8.2(6.4)^{b}	8.0(8.5)^{b}	6.7(5.3)^{b}	<0.001
Platelet (*10^9/L)	433.2±145.1^{a}	409.7±129.6^{a}	437.1±162.6^{a}	354.4±83.8^{ab}	332.7±91.7^{ab}	357.2±134.0^{ab}	289.7±118.8^{b}	70.2±120.2^{c}	195.1±127.3^{c}	327.0±126.1^{ab}	<0.001
Hemoglobin (g/L)	113.7±10.6^{b}	127.9±17.3^{a}	113.1±17.5^{b}	117.3±9.9^{b}	125.3±11.8^{a}	83.0±19.6^{c}	84.2±23.6^{c}	91.0±24.6^{c}	72.1±15.0^{c}	100.5±18.8^{b}	<0.001
Neutrophil ratio	0.61(0.20)^{c}	0.78(0.22)^{b}	0.39(0.30)^{a}	0.47(0.17)^{d}	0.54(0.14)^{ad}	0.54(0.25)^{acd}	0.64(0.21)^{c}	0.33(0.35)^{a}	0.64(0.32)^{c}	0.58(0.20)^{cd}	<0.001
Lymphocyte ratio	0.34(0.19)^{b}	0.16(0.22)^{a}	0.50(0.27)^{c}	0.42(0.48)^{b}	0.37(0.48)^{b}	0.38(0.34)^{b}	0.30(0.18)^{b}	0.22(0.54)^{ab}	0.26(0.38)^{ab}	0.33(0.22)^{abc}	<0.001
Eosinophil ratio	0.01(0.01)^{b}	0.01(0.01)^{bd}	0.04(0.05)^{a}	0.03(0.03)^{c}	0.02(0.03)^{ac}	0.01(0.02)^{bcd}	0.01(0.01)^{bd}	0.01(0.03)^{abcd}	0.01(0.04)^{abcd}	0.03(0.03)^{acd}	<0.001
Eosinophil count (*10^9/L)	0.11(0.17)^{b}	0.11(0.14)^{b}	0.39(0.75)^{a}	0.18(0.21)^{b}	0.15(0.21)^{b}	0.10(0.18)^{b}	0.12(0.10)^{b}	0.11(0.40)^{b}	0.07(0.40)^{b}	0.17(0.22)^{b}	<0.001
PT(s)	12.2(1.1)^{ac}	11.6(1.6)^{bc}	11.7(1.6)^{bc}	11.3(1.1)^{b}	11.3(0.9)^{b}	12.1(1.5)^{abc}	12.0(2.3)^{abc}	12.7(1.8)^{ac}	13.1(2.8)^{c}	12.7(1.4)^{ac}	<0.001
APTT(s)	28.0(6.4)^{bc}	24.0(5.4)^{a}	32.1(7.0)^{bc}	27.8(6.3)^{bc}	28.4(5.4)^{bc}	26.2(5.0)^{a}	24.1(5.4)^{a}	32.5(21.7)^{bc}	28.4(10.1)^{bc}	27.9(6.4)^{abc}	<0.001
D-dimer (mg/L)	0.9(1.2)^{b}	3.5(9.6)^{a}	0.6(0.7)^{b}	0.2(0.1)^{c}	0.2(0.2)^{bc}	0.3(0.6)^{c}	0.5(1.1)^{bc}	1.1(2.7)^{b}	0.4(0.5)^{bc}	0.3(2.2)^{bc}	<0.001
Albumin (g/L)	42.2(5.6)^{bd}	37.7(9.1)^{ac}	39.6(6.4)^{c}	45.2(3.9)^{b}	46.9(4.1)^{b}	38.5(9.6)^{ac}	35.9(9.0)^{ac}	39.0(6.9)^{acd}	31.7(6.4)^{a}	40.5(9.6)^{acd}	<0.001
AST(U/L)	33.4(14.0)^{b}	17.4(16.5)^{cd}	25.1(27.8)^{c}	10.1(16.1)^{d}	12.4(18.7)^{d}	22.1(16.9)^{c}	25.0(12.9)^{c}	18.0(37.4)^{cd}	48.5(71.5)^{a}	18.6(18.8)^{cd}	<0.001
ALT(U/L)	41.2(14.0)^{a}	19.0(10.2)^{c}	35.9(17.6)^{a}	30.0(8.0)^{b}	29.4(13.2)^{b}	28.5(13.7)^{b}	25.5(14.9)^{b}	39.2(51.8)^{a}	55.8(67.0)^{a}	26.3(12.9)^{bc}	<0.001
BUN(mg/dl)	10.4(5.1)^{b}	12.4(8.1)^{c}	6.6(4.4)^{a}	11.4(4.1)^{bc}	11.2(6.1)^{bc}	11.8(7.1)^{bc}	11.9(11.3)^{bc}	11.9(8.7)^{bc}	14.6(13.5)^{c}	11.6(7.6)^{bc}	<0.001
Cr(mg/dl)	0.3(0.1)^{a}	0.4(0.2)^{c}	0.3(0.1)^{a}	0.3(0.1)^{b}	0.4(0.1)^{bc}	0.4(0.2)^{bc}	0.4(0.2)^{bc}	0.3(0.2)^{ab}	0.4(0.1)^{bc}	0.4(0.2)^{bc}	<0.001

Note: WBC: White blood cell; PT: Prothrombin time; APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

For each laboratory index (row), the same superscript letter denotes no statistically significant difference between every two etiologies. For example, there was significant difference in WBC between intussusception (a) and enteritis (b), while no difference between intussusception (a) and HSP (a) because they had a same superscript letter (a).

Table 5: The incidence of BUNCr≥31.5 among different hemorrhage sites [n(%)]

	Hemorrhage site					
BUN/Cr	UGIB	LGIB	Systemic diseases	OGIB	**Total**	***P***
≥31.5	+ 53(58.9)[a]	354(44.6)[ab]	83(37.2)[b]	5(31.3)[ab]	495(44.1)	
	- 37(41.1)[a]	439(55.4)[ab]	140(62.8)[b]	11(68.8)[ab]	627(55.9)	0.004
Total	90(100.0)	793(100.0)	233(100.0)	16(100.0)	1122(100.0)	

Note: The same superscript letter denotes a subset of hemorrhage sites categories whose column proportions do not differ significantly from each other at the 0.05 level.

5. Discussion

Hematochezia is a common symptom presented with complex etiologies. Our results showed intussusception, HSP, enteritis were the top 3 etiologies of hematochezia in children. And the most common etiology in infant and toddler was intussusception; while in older children was HSP, which was quite different from adults. A study from China showed colorectal cancer is the most common etiology of LGIB in adults [9], however, we found in children with hematochezia, solid neoplasms were very rare (0.3%) and none with colorectal cancer.

Intussusception, as the most common etiology of hematochezia in children, accounted for 39.8% of all 1122 cases, which was obviously higher than most western studies. It could be explained by the geographical and racial difference in a certain extent. The incidence of intussusception in Switzerland was 26-38/100,000 [10], whereas it was 181.8/100,000 in China [11]. Meanwhile, we found in children with intussusception, 74% occurred before 1-year-old, and 95% before 3 years old, which was similar to the peak age reported [12].

HSP, an immunoglobulin A-mediated vasculitis, can lead to gastrointestinal hemorrhage caused by mucosal edema, erosion, ulcer and other injuries. HSP was the second etiology of hematochezia, accounting for 14.3%, which was quite different from previous studies. Although its global prevalence ranges from 6.1/100,000 to 70.3/100,000 [13], and a high gastrointestinal involvement was reported [14], we hardly found HSP emphasized as a common etiology in children with hematochezia. Because atypical HSP cases without the onset of skin rashes can be easily misdiagnosed, for the long interval between abdominal pain and rash (up to 7 weeks [15]). During this time, HSP can be early diagnosed by mucosal manifestations of purpura detected by endoscopy. However, some cases may be only diagnosed with gastritis, PU or enteritis, rather than HSP, that's one reason for the low rate of HSP in previous studies.

Enteritis ranked the third cause of hematochezia. For enteritis, infectious factors took up the highest proportion, followed by allergic factors. In local primary medical settings, infectious enteritis was reported as the main cause of LGIB in children [16], however, in tertiary medical referral institutions similar to ours, the constituent ratio of infectious enteritis in LGIB was also relatively low [17]. Because children with diarrhea were mostly treated in local primary medical settings without referral to senior hospital.

Several single-center studies showed that intestinal polyp was the primary cause of hematochezia, accounting for about 49%-57.4% [9, 18]. However, we found intestinal polyp was only the fourth cause. The incidence of intestinal polyp can vary from the geographical, dietary, living habits and genetic factors of subjects. Besides, it's reported intestinal polyp usually occurs in children between 6-7 years old abroad [19], but in our study, the median age was 22 months old and infant was the largest age group. Therefore, the difference of age groups and the low performing rate of colonoscopy in infant could be one reason. Additionally, in older children, results showed HSP was the most common etiology rather than intestinal polyp. We considered the symptom of hematochezia might disappear after the intestinal polyp spontaneously sloughed and healed, leading to an increased negative rate of detection.

Although the Italian Society of Pediatric Gastroenterology considered anal fissure is the common etiology in LGIB in children [20], in our study, perianal diseases were the fifth cause, only accounting for 6.9%. Meanwhile Stampfer L [21] reported anal fissure only accounted for 2.3% in 221 children with hematochezia, lower than our results. This might be related to children with perianal diseases were often not admitted to hospital because they were easily identified and treated in outpatient clinic.

Digestive tract malformation was the sixth cause (5.2%), higher than current reported studies in China (1.1%-2.8%) [9]. The incidence is increasing gradually with each passing year, due to the environmental pollution, improvement in healthcare, and the willing of further examination of parents after a suspicion of deformity. The constituent ratio of digestive tract malformation was close to the incidence of OGIB reported (5%) [20], and hematochezia caused by digestive tract malformation was often attributed to OGIB when examinations failed to locate the bleeding sites. It suggested that digestive tract malformation, especially the "mid-digestive tract" (between the duodenal papilla and ileocecal valve) malformation should be strongly suspected when OGIB was diagnosed. Besides, in digestive tract malformation, Meckel's diverticulum was the most common etiology, and most cases were diagnosed with surgical exploration rather than imageology.

PU, the seventh cause of hematochezia, ranked first among etiologies of UGIB as reported [22]. PU was predominant in adolescent children, of which duodenal ulcer took the majority. Besides, in UGIB, EGV was the second cause, and it was the ninth cause of hematochezia, higher than domestic reports [23]. EGV has a mor-

tality rate of 2.5%~20% [24] and it often leads to excessive bleeding. Therefore, it's important to search for a cause and prevent massive hemorrhage actively. In this study, the mean hemoglobin of EGV was 72.1±15.0g/L and the primary cause of EGV was cavernous transformation of portal vein. However, as the most common cause in UGIB reported [23], gastritis only had a small proportion. This may be related to the negative endoscopic result due to the untimely endoscopic examination as mucosa has a strong self-recovery ability.

Hematological diseases were the eighth etiology, with primary immune thrombocytopenia and leukemia as the dominant diseases. The PLT count (70.2±120.2*109/L) was significantly lower, which played a certain role in clinical

diagnosis.

Wiskott-Aldrich syndrome, a rare X-linked recessive genetic syndrome, accounted for 0.9%, much higher than reported. This may be associated with our resource of patients and acknowledge of this disease. Without hematopoietic stem cell transplantation, children with Wiskott-Aldrich syndrome have a lifespan less than 15 years25, so it's necessary to take possibility of this disease into consideration in children with hematochezia.

Therefore, except for LGIB, UGIB could also lead hematochezia. Our data suggested that LGIB accounted for 70.7%, whereas UGIB only accounted for 8.0%, lower than previous studies (11%)26. It has been reported stool property and BUN/Cr ratio are helpful to diagnose bleeding site of hematochezia. However, there was no difference in BUN/Cr ratio between UGIB and LGIB, although some studies considered the BUN/Cr ≥30 implied UGIB27,28, which suggested whether BUN/Cr ratio can identify UGIB or LGIB could not be confirmed unless larger samples in the hemorrhagic phase are collected and analyzed in further studies.

6. Conclusions

In conclusion, UGIB, LGIB and systemic diseases should be considered as the cause of hematochezia in children. Intussusception, HSP, enteritis were the top 3 etiologies. And etiology varied by age groups, the most common etiology in infant and toddler was intussusception; while in older children was HSP. Stool property, accompanying symptom, radiologic examination and endoscopy were helpful to diagnosis, but BUN/Cr ratio could not differentiate UGIB from LGIB.

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