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The trends of pediatric duodenal ulcer and predictors of recurrence

Pai-Jui Yeh [a,c], Chien-Chang Chen [a], Hsun-Chin Chao [a], Jin-Yao Lai [b], Yung-Ching Ming [b], Mi-Chi Chen [a,c], Ming-Wei Lai [a,c,*]

[a] Division of Pediatric Gastroenterology, Department of Pediatrics, Chang Gung Memorial Hospital, Linkou Branch and Chang Gung University College of Medicine, Taoyuan, Taiwan
[b] Department of Pediatric Surgery, Chang Gung Memorial Hospital, Linkou Branch and Chang Gung University College of Medicine, Taoyuan, Taiwan
[c] Liver Research Center, Chang Gung Memorial Hospital, Linkou Branch, Taiwan

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ABSTRACT

Background: Duodenal ulcer (DU) causes various symptoms in children. The prevalence of *Helicobacter pylori* (Hp)-associated DU has been reducing in some regions, yet the updated trend in Taiwan is unknown. Risk factors of DU recurrence have not been comprehensively investigated in children.
Methods: This retrospective study included children diagnosed with DU to evaluate the demographics, symptoms, diagnostics, treatment, and outcomes. Specific populations (infant, surgery required) were sorted for subgroup analysis. Predictors of DU recurrence was analyzed in patients who received endoscopic follow-ups.
Results: A total of 488 children were included. Most patients were male (72.5%), school-aged (11.3 ± 4.8 years old), and with varied underlying diseases in one-fifth. The annual incidences were around 3–5%, with a declining trend of case numbers and the Hp-positive proportion. Hp infection, concurrent gastric ulcer, perforation, and mortality were noted in 32.7%, 16%, 1.6%, and 1% of patients. Patients with or without Hp infection showed different clinical features but similar outcomes. The characteristics of subpopulations were depicted respectively. Male sex, lower Hb level, and perforation were independent risk factors associated with recurrence.
Conclusions: Hp-positive DU seems to wane. Patients with male sex, lower Hb level, or perforation at diagnosis carried a higher risk of recurrence, which may warrant active surveillance and endoscopic follow-up.

1. Introduction

Duodenal ulcer (DU), as a part of peptic ulcer disease (PUD), refers to a mucosal defect deeper than the muscularis mucosa of the duodenal wall. DU causes variable presentations from asymptomatic, dyspepsia, and upper gastrointestinal (GI) bleeding to perforation [1]. In addition to the two dominating etiologies, *Helicobacter pylori* (Hp) infection and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), other potential factors include acid hypersecretion (Zollinger-Ellison syndrome (ZES)), eosinophilic gastroenteropathy, non-Hp infections, malignancy, ischemic event, medications (corticosteroids, anti-cancer drugs, iron chelators, etc.), Crohn's disease (CD), and other infiltrative diseases [1–7].

Earlier studies of pediatric DU before the 1980s gave limited information on Hp infection status [8–11]. In the 2000s, 11 studies respectively reported their pediatric DU cases and proportion of Hp infection as the following in chronologic order: 30% Hp-positive rate (10 DU cases/622 EGDs, over 6 years, USA, 2001), 71% (7/324, over 2.75 years, Turkey, 2002), 87% (20/521, over 10 years, Saudi Arabia, 2004), 83% (100/732, over 6 years, Japan, 2004), 95.3% (7.2/year, over 6 years, Brazil, 2004), 66.3% (58/751, over 3.5 years, Israel, 2008), 66.7% (57/76, over 10 years, Hong Kong, 2008), 47.7% (40/1234, over 9 years, Taiwan, 2010), 53% (34/732, over 2 years, Europe, 2013), 90.6% (32/307, over 8 years, Chile, 2014), and 47.4% (19/656, over 8 years, Bulgaria, 2018) [12–22]. These results demonstrated a trend (exceptions found in some countries like Chile) of inclining then abating proportion of Hp infection in pediatric DU, corresponding to the emerging body of "non-Hp, non-NSAIDs" PUD [23,24]. Concerning a decreasing global prevalence of Hp, the influence of Hp on pediatric DU is presumably waning [25]. However, there has been a paucity of updated data in the past decade.

The differences between Hp-related and non-Hp DU are of clinical interest. An adult study including 1153 DU patients suggested that concomitant disease and the absence of epigastric symptoms were two

* Corresponding author. Department of Pediatrics and Liver Research Center, Chang Gung Memorial Hospital, 5, Fu-Hsin Street, Guei-Shan District, Taoyuan City, 33305, Taiwan.
E-mail address: a22141@cgmh.org.tw (M.-W. Lai).

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independent predictors for non-Hp non-NSAIDs DU [26]. Elitsur et al. analyzed 10 cases and found no statistical difference in clinical symptoms or endoscopic appearance [12]. Another study suggested that patients with Hp-related PUD had higher mean age and rate of family history, but they enrolled patients with "PUD" instead of exclusive DU [20]. Compared with non-Hp, 20 antral tissues from DU patients with Hp infection harbor more intense mucosal polymorphonuclear cells and a higher level of mucosal interferon-γ [21]. Predisposing factors associated with recurrent DU or perforated DU were primarily discussed in case reports. A comprehensive clinical comparative study with a larger case number is still lacking.

Hence, this study aimed to analyze the clinical presentations, endoscopic features, management, and outcomes of pediatric DU. Characteristics of specific populations (perforated, infantile) and the evolution of Hp association across two decades were also explored.

2. Material and method

2.1. Patients

We retrospectively studied DU patients under 18 years old between Jan 2000 and Oct 2022 at Chang Gung Memorial Hospital, Linkou branch, Taiwan. Patients with the diagnosis were sorted from the electronic record of endoscopic reports and operation records. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB number: 202201901B0).

The diagnosis of DU was established by identifying ulceration through esophagogastroduodenoscopy (EGD) or at surgical repair of duodenal perforation with compatible pathological findings. Patients with substantial missing data were excluded. Medical charts were reviewed to collect demographics, clinical presentations, underlying diseases, endoscopic and laboratory results, medication exposure, treatments (medical, endoscopic, surgical), outcomes, and follow-up status. Laboratory results (white blood cell (WBC) count, hemoglobin (Hb), hematocrit (Hct), platelet (PLT) count, C-reactive protein (CRP), serum gastrin levels nearest to the diagnostic EGD but before any red blood cell (RBC) transfusion were recorded. Hp infection was based on a positive Campylobacter-Like Organism (CLO) test (*Helicotec*UT®Plus, Strong Biotech Corporation, Taipei) or the identification of Hp in pathological exam during the first EGD. Deformity was defined with obstruction, narrowing, or any description of "deformed" duodenal structure in the EGD report. Medication exposure implied the drugs ever prescribed before the DU diagnosis. Anti-Hp therapy referred to the prescription of any suggested regimen for Hp infection [27]. Since EGD is an invasive procedure for young children, follow-up EGD was not routinely arranged except for the indications, including relapsed or unremitted symptoms, a check-up for Hp eradication if other noninvasive tests are not suitable or available, at-risk patients (e.g., long-term NSAID usage), severe first occurrence (massive GI bleeding with hypotension or perforation), or recheck for anatomic obstruction (e.g., pyloric stenosis or antral web). Given the heterogeneity of the follow-up EGD schedule, "resolved" DU was defined as the absence of DU in the first follow-up EGD. "Refractory" or "recurrent" DU was defined as the persistent DU in the first follow-up EGD or resolved DU in the first follow-up EGD with relapse in the subsequent follow-ups, respectively. Refractory or recurrent DU was grouped together in comparison with resolved DU in the risk factor analysis.

2.2. Statistical analysis

Data processing was performed with the Statistical Package for the Social Sciences (SPSS) v. 20 software (SPSS Inc., Armonk, NY, USA). Categorical results were shown as absolute numbers and percentages. Continuous data were expressed as mean ± standard deviation (SD) or the median and interquartile range (IQR) as appropriate. For comparison, independent *t*-test and Mann–Whitney *U* test were employed for continuous variables, while $\chi 2$ and Fisher's exact tests were for categorical variables. Logistic regression models were applied to identify the independent risk factors for recurrence. One-way ANOVA test was used for quadrennial trend analysis from 2007 to 2022. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Patients

Among the 10,721 EGDs performed during the inclusion period, 583 patients were identified using DU as a keyword from the electronic record system. Due to a lack of Hp test or missing data (clinical measures, outcomes, etc.), 95 patients were excluded, 88 from 2000 to 2005, and 7 from the rest period. (Fig. 1).

3.2. Demographic data and underlying diseases

The mean age at diagnosis was 11.3 ± 4.8 years. The male-to-female ratio was 2.6: 1. There were 359 (73.6%) inpatients with a median hospitalization of six days (IQR = 4, 8), while 13.6% of them ever needed intensive care unit (ICU) care.

Eighty-four patients (17.2%) had underlying diseases. Twenty-one patients were diagnosed with Henoch-Schönlein purpura (HSP), 18 patients had portal hypertension (15 associated with biliary atresia), four had CD, two had eosinophilic gastroenteritis, one had necrotizing pancreatitis, and one had Peutz–Jeghers' syndrome (PJS), 16 had a history of abdominal surgeries (including one short bowel syndrome). Other non-gastrointestinal comorbidities included systemic lupus erythematosus (SLE) in four, neurologic (hypoxic-ischemic encephalopathy, epilepsy, cerebral palsy) in 19, and hematological or immunodeficient (leukemia, T cell lymphoma, gastroduodenal lymphoma, Wiskott-Aldrich syndrome, severe combined immunodeficiency) in seven. It is worth mentioning that a patient presenting with DU, hepatic masses, and elevated gastrin level was diagnosed as ZES with liver metastases.

3.3. Clinical presentations

The most prevalent symptoms were abdominal pain (71.3%), vomiting (44.3%), melena (36.9%), hematemesis (21.7%), and dizziness (and weakness) (20.9%). Around 15% of patients had a fever or upper respiratory tract symptoms relevant to NSAID exposure. Details of symptoms are listed in Table 1.

Before EGD, 217 (44.5%) patients had already been prescribed a histamine-2-receptor antagonist (H2RA), 88 (18%) had proton pump inhibitor (PPI) therapy, and 27 (5.5%) had been treated with both. NSAIDs were exposed in merely 11.5% of patients, although incomplete recording was possible.

3.4. Diagnosis

Except for the seven cases undergoing a primary operation for perforation, the rest (98.6%) were diagnosed endoscopically. Around 30% and 10% of DU presented with multiple lesions and duodenal deformity, respectively. The bulb (1st portion) was the most common lesion site (96.3%), involving the anterior and posterior wall in 45.1% and 40%, respectively. Concurrent gastric ulcer (GU) and gastritis were found in 16% and 75% of patients. In particular, Hp infection was documented in 32.8%.

As for laboratory results, anemia was the most recognizable parameter (median 10.5 g/dL, minimum 3.0 g/dL), whereas the rest were generally nonspecific. Gastrin levels were tested in eight patients (range 41.4–8219 pg/mL), with only one diagnosed with ZES.

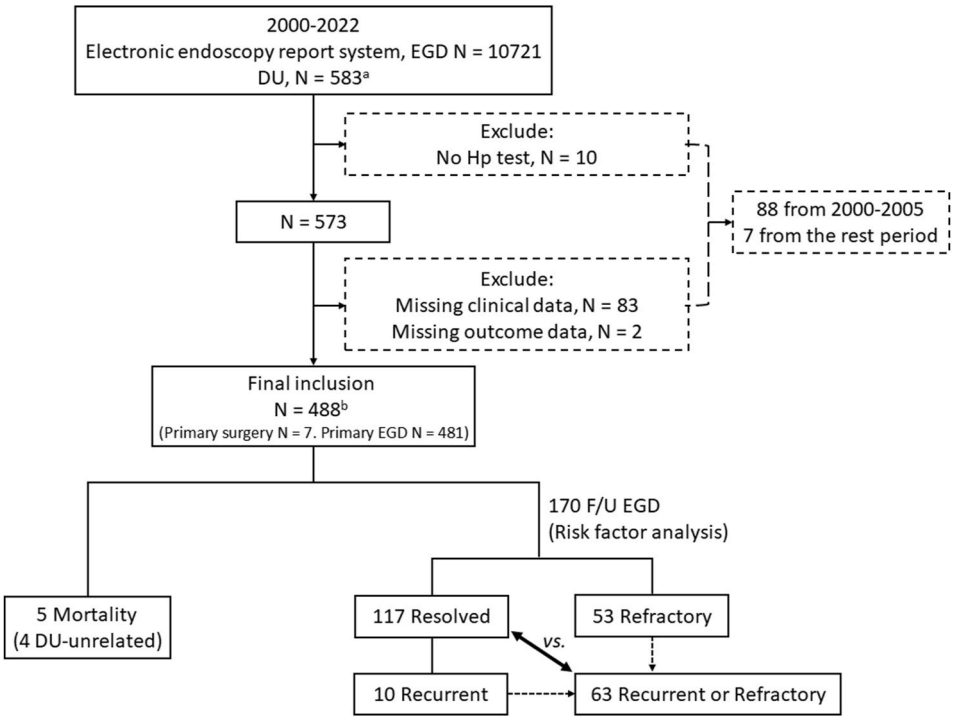

Fig. 1. The flow chart of patient inclusion, exclusion, and outcomes. (DU, duodenal ulcer; EGD, esophagogastroduodenoscopy; Hp, *Helicobacter pylori*; [a], original case number of DU, used for incidence calculation in Fig. 2; [b], final inclusion of DU, used for clinical and risk factor analyses. *vs.* Resolved cases compared with refractory and recurrent patients in risk factor analysis.)

3.5. Treatment

In 26.8% of patients, red blood cell (RBC) transfusion was indicated to correct anemia with hemodynamic instability. PPI (67.8%) surpassed H2RA (35%) in medical treatment, and only 14 patients did not receive either of the two antacids. Anti-Hp therapy was administered in 165 patients, including 11 Hp-negative ones, who were empirically treated under clinical suspicion. Endoscopic treatments were performed in four, comprising of local epinephrine injection in three and hemoclipping in two. Ten (2%) patients ultimately required surgical treatment, including primary repair for DU perforations in eight (vagotomy in one), laparoscopic exploration for GI bleeding survey in one, and surgical correction for luminal obstruction in one (subtotal gastrectomy, Billroth I gastroduodenostomy, duodenoduodenostomy) (Table 1, section "Treatment").

3.6. Outcomes and follow-up

The median duration of hospitalization was 6 days. Among the five in-hospital mortalities (1%), one patient with underlying status epilepticus died of refractory GI bleeding, while the rest were not DU-related (multiple organ failure).

A total of 170 patients (34.8%) underwent at least one EGD follow-up, with the first follow-up EGD at a median interval of 5 months. One hundred and seventeen patients (68.8%) achieved DU resolution in the 1st follow-up, whereas 53 patients still had DU (refractory). Ten patients among the resolved DU eventually encountered recurrence (refractory + recurrent = 63, 37.1%) (Fig. 1). Hp infections were documented in 11 (17.5%) of these refractory or recurrent DU. These patients were retreated with the 2nd line antibiotic regimens according to the guidelines because Hp culture and drug sensitivity test were unavailable in our center.

3.7. Trends of duodenal ulcer incidence and Helicobacter pylori proportion

Fig. 2 demonstrates the annual DU case numbers, incidence, and the proportion of Hp-positive status. The incidence of DU was expressed as the annual case number divided by the total EGD number. The original DU case numbers were applied to calculate the incidence to reflect the authentic trend. Yet, the Hp-positive proportion from 2000 to 2005 was potentially underestimated since some cases missed the Hp test, which is demonstrated in a light-colored line in Fig. 2.

After reaching a peak in 2005, the DU annual case numbers gradually but significantly descended despite a minor rebound in 2019 ($p = 0.023$, ANOVA test for quadrennial trend analysis). Before 2005, the incidence was around 6–9%; however, it descended and remained about 3–5% afterward. The Hp-positive proportion declined from >50% in 2007~2008 to 15–35% between 2009 and 2022, except for a rebound to 50% in 2017 ($p = 0.349$).

3.8. Special populations – infantile DU, surgical DU, and HSP

Twenty-four infants (below 1.5 years old) were included, with an average age of 0.81 ± 0.43 years, and the youngest was 1-week-old (Table 2). The male-to-female ratio was close to the whole cohort (2.4: 1). Eleven patients (45.8%) had critical illness or underlying diseases. They had longer admission duration (median, 10 days), more RBC transfusions (58.3%), and markedly higher ICU needs (76.5%). The proportions of concurrent GU, deformity, multiple ulcers, and lesion distribution were similar to the whole cohort. However, there was only one Hp-positive patient (4.2%) and one perforation. The major symptoms for infants were hematemesis/tarry stool and vomiting, and they had a lower Hb/Hct level compared to the elder group (median 8.35 g/dL vs. median 10.5 g/dL). The outcomes were relatively favorable, with one non-Hp recurrence, one surgical need, and no mortality.

Ten patients required surgical treatment (Table 3), and seven initially presented with perforation. One patient (#10) had perforation

Table 1
Demographics, manifestations, treatments, and outcomes of 488 DU patients.

Demographics			
Age (year, mean ± SD)	11.3 ± 4.8	Inpatient (n (%))	359 (73.6)
Sex	M: F = 2.6:1	ICU (n (%))	49 (10)
Underlying diseases (n (%))			
GI system		HSP	21 (4.3)
PHTN[a]	18 (3.7)	IBD	4 (0.8)
Abdominal surgery	16 (3.3)	Others (EG, NP, PJS)	4 (0.8)
Non-GI system	54 (11.1)		
No comorbidity	404 (82.8)		
Presentations (n (%))			
Abdominal pain	348 (71.3)	Fever	73 (15)
Vomiting	216 (44.3)	URI symptoms	63 (12.9)
Melena	180 (36.9)	Dizziness/weakness	102 (20.9)
Hematemesis	106 (21.7)	Pallor	47 (9.6)
Fullness	45 (9.2)	Shock	46 (9.4)
Diarrhea	43 (8.8)	Syncope	20 (4.1)
Endoscopic and surgical findings (n (%))			
Hp infection	160 (32.7)	1st portion (bulb)	470 (96.3)
Multiple DUs	147 (30.1)	Bulb _A	212 (45.1)
Deformity	48 (10)	Bulb _P	187 (40)
Perforation	8 (1.6)	Bulb _GC	42 (8.9)
Gastritis	364 (75)	Bulb _LC	8 (1.7)
Gastric ulcer	78 (16)	2nd portion	31 (6.4)
Laboratory tests (median (IQR))			
WBC (1000/μL)	8.4 (6.5, 12.1)	Platelet (1000/μL)	289 (236.5, 381)
Hb (g/dL)	10.5 (7.5, 13.3)	CRP (mg/L)	5.2 (1.4, 25.3)
Medication exposure before diagnosis (n (%))			
PPI	88 (18)	NSAIDs	56 (11.5)
H2RA	217 (44.5)	Steroids	34 (7)
Antibiotics	64 (13.1)	Immunosuppressant	4 (0.8)
Treatment (n (%))			
PPI	331 (67.8)	RBC transfusion	131 (26.8)
H2RA	171 (35)	Local treatment	4 (0.8)
Hp therapy	165 (33.8)	Operation	10 (2)
Course			
Admission (n (%))	359 (73.6)	Admission (day, IQR)	6 (4, 8)
ICU need (n (%))	49 (10)		
EGD FU (n (%))	170 (34.8)	Time to FU (day, IQR)	153 (86, 359)
Outcomes (n (%))			
Resolved at 1st FU EGD	117 (68.8)	Refractory or recurrence	63 (37.1)
Death	5 (1)		

Abbreviations: A, anterior wall; BA, biliary atresia; CRP, c reactive protein; EG, eosinophilic gastroenteritis; EGD, esophagogastroduodenoscopy; F, female; FU, follow-up; GC, greater curvature; H2RA, histamine-2-receptor antagonist; Hb, hemoglobin; Hp, *Helicobacter pylori*; HSP, Henoch-Schönlein Purpura; IBD, inflammatory bowel disease; ICU, intensive care unit; IQR, interquartile range; LC, lesser curvature; M, male; NP, necrotizing pancreatitis; NSAID, non-steroidal anti-inflammatory drug; P, posterior wall; PHTN, portal hypertension; PJS, Peutz–Jeghers' syndrome; PPI, proton pump inhibitor; RBC, red blood cell; SD, standard deviation; URI, upper respiratory infection; WBC, white blood cell.

[a] Including 15 patients with biliary atresia.

after endoscopy. They presented with a similar age range to the entire cohort, yet a more substantial male predominance (M: F = 4:1). Five patients required ICU care, and among them, three with underlying diseases, including one SLE patient complicated with multiorgan failure, an infant with severe acute malnutrition, and an EBV-infected patient with respiratory distress and pericardial effusion. DU was located in the 1st portion in 9 patients and both the 1st and 2nd portion in one, while one patient combined with GU. Only one patient had an Hp infection proved by preoperative endoscopy. All eight perforations developed in the 1st portion. Due to perforation with pneumoperitoneum and peritonitis, the majority presented with abdominal pain, whereas GI bleeding was noted in one-third. They were treated with PPI post-surgery. Among the eight patients who received follow-up endoscopy around two months after surgery, seven still had DU, and two of them were tested positive for Hp. In total, three of the ten patients who required surgery had Hp infection.

Twenty-one patients were documented with confirmed or highly suspected HSP concurrently. They were younger (8 ± 3.2 years) and presented with a higher proportion of multiple lesions (66.7%), more duodenal second portion involvement (42.9%), less occurrence of GI bleeding, and no Hp infection. Given the absence of ICU need, no mortality, and a low recurrent rate (4.8%), the prognosis in this subgroup seemed favorable.

3.9. Differences between Hp-positive and Hp-negative DU

As shown in Table 4, these two subsets of patients manifested variably. Patients with Hp-positive DU were older and more male-predominated. They tended to present with melena, syncope, and less systemic symptoms (fever, URI). The ulcer involved the bulb more than the second portion and caused a higher risk of deformity. They had less elevated inflammatory markers (WBC, CRP) but lower Hb levels. Although the Hp-positive group had a significantly shorter admission duration and lower ICU need, the overall prognosis (surgery, recurrence, and mortality) was comparable.

3.10. Risk factor analysis for DU recurrence

Risk factor analysis for refractory or recurrent DU was performed in 170 patients with at least one EGD follow-up. Four independent parameters were associated after multivariable logistic regression analysis (Table 5). Male, lower Hb level, and perforation were risk factors for refractory or recurrence, while hematemesis showed a possible reverse effect.

Subgroup analyses of baseline characteristics and treatment were performed to clarify the influence of hematemesis (Supplementary Table 1). Patients in the hematemesis group had higher chances of hospitalization, shock, and thus empiric therapy with PPI or H2RA before EGD. In addition, a significantly higher proportion of this group was treated with PPI or blood transfusion.

4. Discussion

DU is an important etiology of acute abdomen in children. This study included 488 cases over two decades, which is the largest cohort to date focusing on pediatric DU. In addition to patient characterization and a comprehensive comparison regarding Hp status, we further assessed vulnerable subpopulations (infantile, surgery required) and first proposed clinical predictors for pediatric DU with refractory course or recurrence.

As several studies suggested a declining global incidence of PUD till 2010, the incidence and trend of pediatric DU in the past decades were unclear [28]. In 2004, Kawakami et al. reported the incidence was estimated 4–7.2 cases/year in large medical centers [16]. A European multicenter pediatric study in 2007 reported the incidence of DU and duodenal erosion were 1% (7 cases/694 EGDs) and 2.2% (15/694), respectively [29]. Previous cohort studies reported a range of pediatric DU at around 1.6–13.7 (cases/EGDs), depending on the country, study year (2001–2018), and test indications [12–22]. Our data demonstrated a relatively constant annual incidence of approximately 3–5% (cases/EGDs), although the crude number has fallen, possibly due to the dropping pediatric population and the coronavirus pandemic. Compared to the incidence of 3.2% (40/1234 cases/EGDs) reported by a Taiwanese study in 2010 (1999–2008), the epidemiologic status has not

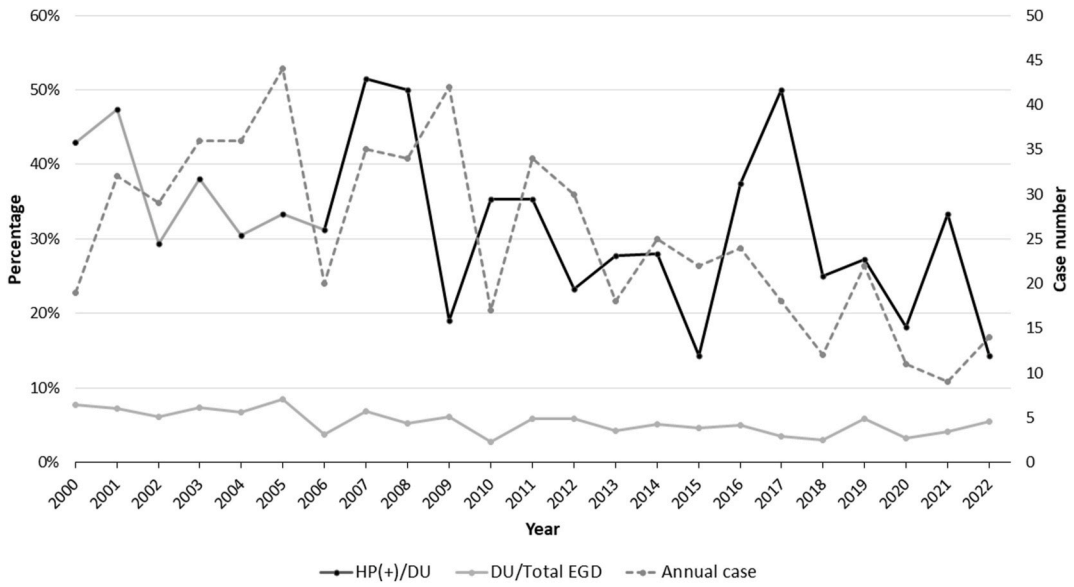

Fig. 2. The annual case numbers, incidence, and proportion of *Helicobacter pylori* infection of pediatric duodenal ulcers since 2000. The Hp-positive proportion line from 2000 to 2005 is light-colored to indicate potential underestimation due to missing Hp tests. (DU, duodenal ulcer; EGD, esophagogastroduodenoscopy; Hp, *Helicobacter pylori*.)

Table 2
Differences of duodenal ulcer between infantile and non-infantile patients.

	Infantile (N = 24)	Non-infantile (N = 464)	p-value
Sex (M: F)	17:7	337:127	0.848
Inpatient (N, %)	24 (100)	335 (72.2)	0.001[b]
ICU (N, %)	13 (54.2)	36 (7.8)	<0.001[c]
Abdominal pain (N, %)	3 (12.5)	345 (74.4)	<0.001[b]
Vomiting (N, %)	13 (54.2)	203 (43.8)	0.316
Melena (N, %)	20 (83.3)	160 (34.5)	<0.001[b]
Hematemesis (N, %)	11 (45.8)	95 (20.5)	0.003[c]
Fever (N, %)	9 (37.5)	64 (13.8)	0.001[c]
URI symptoms (N, %)	5 (20.8)	58 (12.5)	0.235
Dizziness/weakness (N, %)	1 (4.2)	101 (21.8)	0.039[b]
Syncope (N, %)	0 (0)	20 (4.3)	0.615
Multiple DU (N, %)	7 (29.2)	140 (30.2)	0.917
Deformity (N, %)	2 (8.3)	46 (9.9)	1.000
Perforation (N, %)	1 (4.2)	6 (1.3)	0.299
Gastritis (N, %)	16 (66.7)	348 (75)	0.361
Gastric ulcer (N, %)	4 (16.7)	74 (15.9)	1.000
Hp (N, %)	1 (4.2)	159 (34.3)	0.001[b]
1st portion (bulb) (N, %)	23 (95.8)	447 (96.3)	0.603
2nd portion (N, %)	2 (8.3)	29 (6.3)	0.659
WBC (1000/μL) (mean ± SD)	12716.7 ± 5490.4	9687.5 ± 5414.7	0.008[a]
Hb (g/dL) (mean ± SD)	8.1 ± 2.6	10.5 ± 3.3	<0.001[a]
CRP (mg/L) (mean ± SD)	10.5 ± 22.6	28.2 ± 55.3	0.170
Admission (day) (mean ± SD)	30.5 ± 69.3	9.9 ± 30	<0.001[a]
Recurrence (N, %)	1 (4.2)	62 (13.4)	0.344
Operation (N, %)	1 (4.2)	9 (1.9)	0.399
Death (N, %)	0 (0)	5 (1.1)	1.000

Abbreviations: CRP, c reactive protein; DU, duodenal ulcer; F, female; Hb, hemoglobin; Hp, *Helicobacter pylori*; ICU, intensive care unit; M, male; URI, upper respiratory infection; WBC, white blood cell.

[a] Student t-test.
[b] Fisher exact test.
[c] X^2-test.

significantly changed in the past two decades in Taiwan.

Concerning etiologies, over half of our patients were "Hp-negative and NSAID-negative" DU. In parallel with the declining pediatric prevalence rate of Hp infection in Taiwan, the Hp-positive DU also gradually decreased [30]. On the other hand, the patients exposed to NSAIDs (11.5%) or other ulcerogenic medications (corticosteroids: 7%, immunosuppressant: 1%) accounted for less than 20%. As for NSAIDs, the prescription frequency also exhibited a lowering trend, from 29% (as antipyretics in a study of pediatric DU) in 1989 to 14.9% in 2010 [11,20]. Due to the eradication of Hp and prudent prescription of NSAIDs, "idiopathic" PUDs are gaining more weight and impact since Hp-negative PUDs may encounter a higher risk of relapse [23]. Hp-negative group may comprise up to 70% of DU in some research from developed countries, all supporting a similar trend in Taiwan as our study. Associations of Hp-negative and NSAID-negative DU include false-negative diagnostic assays, complicated DU, isolated Hp duodenal colonization, ZES, and concomitant comorbidities, etc [31]. Comorbidities and the absence of epigastric symptoms may predict Hp-negative, NSAID-negative DU in adult patients [26]. However, there is a lack of research characterizing "idiopathic" DU in children [12,20]. Our patients in the Hp-positive and Hp-negative groups present some different clinical features, even though the outcomes were comparable. The younger age, more prevalent nonspecific symptoms, and a higher ICU need in the Hp-negative group denoted a multisystemic predisposing status. In contrast, the Hp-positive group was prone to "hemorrhagic" features (melena, syncope, anemia). Histopathological, microbiome, and GWAS studies have disclosed specific features associated with Hp infection, which may shed light on the pathophysiology of DU in the future [21,32,33]. Besides Hp and medication, one-fifth of our patients had diverse underlying diseases likely linked to DU. Portal hypertension predisposes to DU, especially in patients presenting with variceal bleeding [34]. Around 20–30% of pediatric CD patients have upper GI involvement, and the histopathological features may help differentiate CD-related DU [35–37]. Another noteworthy disease is HSP, a common leukocytoclastic vasculitis in childhood with GI involvement in 50–85% of patients [38,39]. The ulcerogenic mechanism of HSP is hypothetically contributed by vasculitis-induced ischemia, intramural hemorrhage, and IgA deposit [40]. Further than previous case reports, our data presented a substantial number of HSP-associated DU cases to corroborate the preference for duodenal second-portion involvement and a fair prognosis with corticosteroid therapy [40,41].

Our patients were averagely school-aged and male-dominated, similar to prior demographic observations [8,11,18,20]. Noteworthily,

Table 3
Characteristics of 10 duodenal ulcer patients receiving surgeries.

	Sex	Age (yr)	ICU	Hp[a]	Symptom	OP method	Hp[b]/DU	Death	Remarks
1	M	11.3	N	Neg	P,V,H,Fe,U	Subtotal gastrectomy Billroth I procedure	Neg/**Y**	N	Hx of DU, post pyloroplasty, and vagotomy
2	M	4.8	N	–	P,U	Primary repair	Neg/**Y**	N	
3	F	15.2	**Y**	**Pos**	Me	Check bleeder	–	N	Prolonged GI bleeding
4	M	16.9	N	–	P,U	Primary repair & Vagotomy	**Pos**/**Y**	N	
5	F	15.9	**Y**	–	P,H,Me	Primary repair	Neg/**Y**	**Y**	SLE, multiorgan failure
6	M	15.8	**Y**	–	P,V	Primary repair	Neg/**Y**	N	
7	M	12.6	N	–	P,V,Fe,U	Primary repair	Neg/N	N	
8	M	10.7	**Y**	–	P,Fe,U	Primary repair	Neg/**Y**	N	EBV infection
9	M	13	N	–	P	Primary repair	**Pos**/**Y**	N	
10	M	0.2	**Y**	Neg	Me	Primary repair	–	N	SAM and severe anemia

Abbreviations: DU, duodenal ulcer; EBV, Epstein-Barr virus; F, female; Fe, fever; GI, gastrointestinal; H, hematemesis; Hp, *Helicobacter pylori* [a]status at preoperative endoscopy, [b]status at postoperative endoscopy; Hx: history; ICU, intensive care unit; M, male; Me, melena; OP, operation; P, abdominal pain; SAM, severe acute malnutrition; SLE, systemic lupus erythematosus; U, upper respiratory tract symptom; V, vomiting; yr, year;—: not done; Neg: negative; Pos: positive.

Table 4
Differences in clinical features between DU patients with or without *Helicobacter pylori* infection.

	HP-positive (N = 160)	HP-negative (N = 328)	p-value
Age (yr) (mean ± SD)	12.9 ± 2.9	10.5 ± 5.3	<0.001[a]
Sex (M:F)	3.7:1	2.3:1	0.032[§]
Inpatient (N, %)	60 (37.5)	170 (51.8)	0.092
ICU (N, %)	5 (3.1)	44 (13.4)	<0.001†
Abdominal pain (N, %)	117 (73.1)	231 (70.4)	0.536
Vomiting (N, %)	71 (44.4)	145 (44.2)	0.972
Melena (N, %)	70 (43.8)	110 (33.5)	0.028[c]
Hematemesis (N, %)	36 (22.5)	70 (21.3)	0.771
Fever (N, %)	3 (1.9)	70 (21.3)	<0.001[c]
URI symptoms (N, %)	12 (7.5)	51 (15.5)	0.013[c]
Dizziness/weakness (N, %)	56 (35)	46 (14)	<0.001[c]
Syncope (N, %)	13 (8.1)	7 (2.1)	0.002[c]
Multiple DU (N, %)	55 (34.4)	92 (28)	0.153
Deformity (N, %)	26 (16.3)	22 (6.7)	0.001[c]
Perforation (N, %)	0 (0)	7 (2.1)	0.102
Gastritis (N, %)	126 (78.8)	238 (72.6)	0.14
Gastric ulcer (N, %)	25 (15.6)	53 (16.2)	0.88
1st portion (bulb) (N, %)	160 (100)	310 (94.5)	0.001[b]
2nd portion (N, %)	1 (0.6)	30 (9.1)	<0.001[b]
WBC (1000/μL) (mean ± SD)	8.9 ± 2.9	10.3 ± 6.3	0.002[a]
Hb (g/dL) (mean ± SD)	9.6 ± 3.3	10.8 ± 3.3	0.002[a]
CRP (mg/L) (mean ± SD)	9.1 ± 15.8	30.4 ± 57.9	<0.001[a]
Admission (day) (mean ± SD)	5.5 ± 2.7	13.8 ± 32.4	<0.001[a]
Recurrence (N, %)	26 (16.3)	37 (11.3)	0.124
Operation (N, %)	1 (0.6)	9 (2.7)	0.177
Death (N, %)	0 (0)	5 (1.5)	0.178

Abbreviations: CRP, c reactive protein; F, female; Hb, hemoglobin; HP, *Helicobacter pylori*; ICU, intensive care unit; M, male; SD, standard deviation; URI, upper respiratory infection; WBC, white blood cell; yr, year.

[a] Student t-test.
[b] Fisher exact test.
[c] X^2-test.

we evaluated a group of 24 infantile DU, which lacks comprehensive literature due to rare incidences. All the infants were endoscopically diagnosed, and three of them were less than one month of age. A neonatal series showed DU in 1.9% of 52 scope-examined cases as the cause of upper GI bleeding [42]. A 16-infant series younger than 11 weeks old successfully diagnosed PUD by barium meals (12), endoscopy (1), and surgery (1) [43]. However, infantile DU seemed not to implicate clinical complexity such as outcomes or underlying diseases. Infants were less likely to be associated with Hp and NSAIDs than the elder group. Prior studies proposed some factors with increasing risk of GI bleeding in infants, such as prematurity, sepsis, coagulopathy, hypovolemia, etc., but none were present in our patients. The mechanism of infantile DU needs further study.

The incidence of surgical or perforated pediatric DU is unclear. As prior studies proposed a 2–10% perforation rate for PUD, our study found a 1.6% perforation rate [1]. As for risk assessment, the male gender imposes a high risk since male predominance was 80% in our perforated cases and 100% in Yan et al.'s series [44]. In their series of 11 children, dexamethasone use was the most common risk factor for duodenal perforation [44]. Other adult PUD studies regarded aging, NSAID use, Hp infection, smoking, and acute stress as risk factors for perforation [45]. Intriguingly, our patients did not possess these features. Delayed diagnosis and management lead to a worse prognosis [46]. Hence, abrupt pneumoperitoneum must be promptly evaluated for perforated DU, especially if any risk factor exists.

Given the invasiveness of endoscopy and the side effects of prolonged PPI use, risk stratification of DU recurrence is in demand yet unclarified. Factors associated with PUD recurrence in adults include Hp infection, male gender, smoking, alcohol, previous recurrence, history of complication, genetic polymorphism, bulb deformity, and gastric metaplasia of duodenal mucosa [47–51]. An adult study on the Hp-negative population found that PUD recurrence was associated with age, male gender, and chronic kidney disease [52]. However, some of the factors remain controversial [53,54]. For pediatric DU, we proposed four potential predictors: male, anemia, perforation, and hematemesis based on this study. The male preponderance has been attributed to the estrogen-regulated duodenal bicarbonate secretion and its protective effect in females. Still, it is unclear whether this model applies to prepubertal children [55]. Significant anemia and perforation implied disease severity, which may predispose to recurrence. On the contrary, patients with hematemesis had significantly less recurrence, which might be explained by their early commencement and continued therapy of PPI. As suggested in some reviews, PPI and H2RA reduce DU recurrence compared to a placebo, and history of PPI use decreases the chance of PUD rebleeding [53,56,57]. In brief, male patients, significant anemia or perforation at diagnosis may encounter a higher risk of refractory or recurrent DU, warranting optimal ulcer treatment and endoscopic follow-ups. Besides, patients exhibiting hematemesis may benefit from aggressive and timely antacid therapy and transfusion, which may reduce the recurrence risk. Future studies with longer follow-ups are required to validate the applicability of these risk predictors.

The strengths of the study lie in its large cohort size that allowed a comprehensive analysis of the trends of DU, Hp proportion, and unique subpopulations (surgical DU, infantile, HSP). It is also the first study exploring the risk prediction for pediatric refractory or recurrent DU. Still, limitations arose from its retrospective design, cohort

Table 5
Logistic regression analysis of risk factors for refractory or recurrent DU.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.047	0.976–1.123	0.204			
Sex (male)	2.371	1.044–5.385	**0.039**	3.43	1.126–10.448	**0.03**
ICU	0.641	0.217–1.892	0.421			
IBD	0.869	0.077–9.781	0.909			
PHTN	0.341	0.094–1.239	0.102			
HSP	0.426	0.047–3.901	0.45			
HP	1.351	0.708–2.579	0.361			
Multiple DU	1.131	0.576–2.219	0.72			
Gastric ulcer	0.594	0.257–1.376	0.225			
Deformity	1.241	0.498–3.095	0.643			
Perforation	9.386	1.071–82.283	**0.043**	20.234	1.943–210.749	**0.012**
Abd pain	1.644	0.801–3.373	0.175			
Vomiting	0.572	0.3–1.094	0.091			
Hematemesis	0.239	0.087–0.655	**0.005**	0.183	0.058–0.571	**0.003**
Melena	1.115	0.574–2.167	0.749			
Hb	0.862	0.776–0.957	**0.006**	0.827	0.734–0.932	**0.002**
Platelet	1.003	1.001–1.005	**0.016**	1.002	1–1.005	0.074
CRP	1.006	0.998–1.014	0.127			

Abbreviations: Abd, abdominal; CI, confidence interval; CRP, c reactive protein; DU, duodenal ulcer; Hb, hemoglobin; HSP, Henoch-Schönlein Purpura; IBD, inflammatory bowel disease; ICU, intensive care unit; OR, odds ratio; PHTN, portal hypertension.

characteristics (tertiary medical center), subjective symptomatic descriptions, and interindividual differences in endoscopic interpretation and clinical management. The pre-diagnosis use of PPI and antibiotics may lead to underestimated Hp incidence. Since the risk factor analysis was performed on patients with endoscopic follow-up, the results may not be generalized to the entire DU population.

5. Conclusion

Despite a steady annual incidence of DU over two decades, Hp-positive proportion in pediatric DU was declining. Most patients were male, school-aged, and one-fifth had varied underlying diseases. Hp infection status did not significantly alter the outcomes. Infants with DU may have more extended hospitalization, transfusion needs, and ICU care but comparable outcomes with older patients. Patients with male sex, lower Hb level, or perforation at diagnosis carried a higher risk of recurrence, which may warrant active surveillance and endoscopic follow-up.

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Study design: PJY, MWL; Data curation and methodology: CCC, HCC, JYL, YCM, MCC; Data analysis: PJY; Manuscript drafting: PJY; Critical review: MWL.

Consent statement

Not required.

Declaration of competing interest

The authors disclose no potential sources of conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2024.04.011.

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