Usefulness of a Serological Panel Test in the Assessment of Gastritis in Symptomatic Children

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Key Words

IgG anti-*H. pylori* antibodies • Serum pepsinogens I and II • Gastrin-17 • *Helicobacter pylori* • Gastritis

Abstract

Background: Non-invasive methods are advisable for the detection of *Helicobacter pylori*-related chronic gastritis in pediatric patients. Serum pepsinogens I and II (sPGI and sPGII), gastrin-17 (G-17) and anti-*H. pylori* antibodies (IgG-*Hp*) have been proposed as a 'serological gastric biopsy'. **Aim:** To assess *H. pylori* infection and to evaluate gastric mucosa status in a pediatric population by means of serological parameters such as sPGI, sPGII, G-17 and IgG-*Hp*. **Methods:** 45 consecutively children evaluated for upper gastrointestinal symptoms were analyzed. All children were submitted to upper gastrointestinal endoscopy with biopsies. Serum samples were analyzed for IgG-*Hp*, sPGII, sPGI and G-17 (Bio-hit, Helsinki, Finland). **Results:** 18 children had *H. pylori*-related mild or moderate non-atrophic chronic gastritis. They presented significantly higher mean levels of sPGII and of IgG-*Hp* than negative ones, either under or up to 10 years. sPGI showed significantly increased levels in *H. pylori*-positive patients only over 10 years. G-17 levels were not differ-

ent between *H. pylori*-positive and -negative ones. The best cut-offs of IgG-*Hp*, sPGII and of product IgG-*Hp*•sPGII, to identify *H. pylori* infection, were 30 IU/l, 9 µg/l, and 241 IU/l•µg/l, respectively. The product IgG-*Hp*•sPGII identified *H. pylori* infection with a 100% sensitivity, 92% specificity, 90% positive predictive value and 100% negative predictive value. IgG-*Hp* and IgG-*Hp* showed a correlation ($r = 0.94$; $p < 0.001$). **Conclusions:** Combined analysis of sPGII and IgG-*Hp* antibody levels could be recommended as a non-invasive panel for the assessment of *H. pylori*-related histological alterations of gastric mucosa in childhood.

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Introduction

Helicobacter pylori infection is known to be acquired primarily during childhood [1]. In the last 30 years, the prevalence of this infection has dramatically changed in developed countries, with a marked decrease of infected children (<10% in some countries) by the age of 10 years, remaining very high in developing countries (up to 80% of infected children <5 years) [2]. However, this prevalence is quite elevated (ranging from 22 to 45%) also in

developed countries, when a population of symptomatic children is considered [3, 4].

In both adults and children [5, 6], *H. pylori* infection is responsible for the majority of chronic gastritis and its action predispose to severe diseases such as peptic ulcer and gastric malignancies. Ulcer disease is prevalently related to *H. pylori* infection, although it develops in a small number of infected children [7]. The infection is, also, a risk factor for mucosa-associated lymphoid tissue (MALT) lymphoma both in adults and children as well for primary gastric cancer in adults [8]. Moreover, early acquisition of the infection is considered a risk factor for development of gastric cancer in adulthood [9]. On the other hand, the role of *H. pylori* in children with recurrent abdominal pain or non-ulcer dyspepsia remains unclear [10–13].

According to international guidelines [6, 14, 15], in children with severe upper gastrointestinal symptoms, endoscopy with biopsies is the gold standard to diagnose organic disease and *H. pylori* infection. On the other side, a non-invasive test is proposed in epidemiologic studies, in efficacy monitoring of *H. pylori* treatment and in patients who refuse endoscopy.

Among the available non-invasive tests, the most current used are: detection of *H. pylori* antibodies from different substrates (serum, saliva and urine), stool antigen research and ^{13}C -urea breath test. Enzyme-linked immunosorbent assays, to detect *H. pylori* antibodies in whole blood, plasma and serum, are relatively inexpensive and easy to perform. However, compared with histology, they have not sufficiently high sensitivity and specificity both in adults and children and are not recommended as a unique means of diagnosing *H. pylori* infection [14]. In young children the serologic response may be weak or absent [16, 17]. Furthermore, it does not distinguish between actual and previous infection because the antibody titer decreases very slowly after cure [18]. False-positives may also occur after spontaneous [19] or previous eradication [20].

H. pylori stool antigen test is validated to screen for *H. pylori* infection in adults [5] and it is promising in children [21], particularly if the new monoclonal enzyme immunoassay [22] is used. However, additional pediatric studies evaluating the accuracy of this test are required [23, 24]. The ^{13}C -UBT has excellent performance both in adults [25] and children [26]. However, the results could be influenced by concurrent use of drugs (antimicrobials or gastric antisecretory) or by the presence of other urease-producing organisms. This test, moreover, is expensive and requires air sampling with a facemask, which is

technically more difficult to perform and potentially unpleasant in young children. Finally, the ^{13}C -urea breath test has not been validated in a sufficient number of young children (especially <2 years of age) [27].

No single test, either invasive or non-invasive, is fully reliable, and even histology is not positive in 100% of cases [28]. Furthermore, all of the non-invasive tests do not give any information about morphological and functional status of gastric mucosa.

Morphological abnormalities of the gastric mucosa may be associated with various disturbances of gastric secretion. Indeed, prior to the discovery of *H. pylori*, Samloff et al. [29] reported that the inflammation of the gastric mucosa was associated with alterations in pepsinogens I and II secretion. It is well known that serum pepsinogen I (sPGI) and II (sPGII) increase in *H. pylori*-related non-atrophic chronic gastritis in adults [30, 31] as well in children [32, 33] and their concentrations decrease after eradication therapy [34–36]. In particular, sPGII seems to better correlate with the severity of inflammation [33, 34, 37]. Conversely, very low values of sPGI associated with altered levels of G-17 (increased or decreased) are well demonstrated in adults to be correlated with atrophic damages of gastric mucosa [38]. These pathologic features are rare in children [39, 40], although their presence is not completely excluded in a pediatric population, as observed in some recent studies [41, 42]. Therefore, a panel of four serological tests such as sPGI, sPGII, gastrin-17 (G-17) and anti-*H. pylori* antibodies (IgG-*Hp*) could be proposed in the first evaluation of children with upper gastrointestinal symptoms as performed by Kalach et al. [43].

The aim of the present study was to evaluate, in a population of children, *H. pylori* infection and gastric mucosa status by means of serological parameters such as sPGI, sPGII, G-17, and IgG-*Hp*, and to explore the accuracy of these tests in comparison to endoscopy with biopsy.

Materials and Methods

A series of 45 consecutive children (19 males, 26 females, mean age 10.4, range 3–17 years) were referred to Department of Pediatrics, University of Parma, Parma, Italy, for epigastric pain associated or not with vomiting. None of the children had been previously treated for *H. pylori* infection or had taken antibiotics, acid-suppressive drugs (H_2 -receptor, proton pump inhibitors, antacids, bismuth preparations) within the previous month. Children with celiac disease, renal failure or gastric surgery were excluded from the study. Informed consent was obtained from the parents.

Assessment of *H. pylori* Status

At baseline, each patient underwent upper gastrointestinal endoscopy with 6 biopsies for histological examination (3 from the antrum, 3 from the corpus), 1 for microbiological analysis and 1 for the rapid urease test. Serial sections (5 µm thick) prepared from formalin-fixed biopsy samples were embedded in paraffin and stained with hematoxylin and eosin for conventional histological analysis and with modified Giemsa for the detection of *H. pylori*. The Updated Sydney System classification was used to assess the grade of gastritis [44]. The rapid urease test (Helori Urease, Eurospital, Trieste, Italy) was performed with antrum samples; the reaction was considered positive when the reagent turned from yellow to red magenta, thus indicating the presence of *H. pylori*. For culture, mucosal biopsies from antrum were placed on agar plates and incubated at 37°C with 5% CO₂ and 100% humidity for 7 days. The *H. pylori* status was assessed by at least two positive tests: histology, rapid urease test (CLO test) and culture.

Determination of sPGL, sPGII, G-17 and IgG-Hp Levels

Blood samples (5 ml venous blood) were taken from each child on the first day of examination prior to endoscopy. These samples were stored before analysis and then centrifuged at -20°C. sPGL, sPGII, serum G-17 and IgG-Hp levels were determined with enzyme-linked immunosorbent assays (Biohit, Helsinki, Finland), according to the manufacturer's instructions.

Statistical Analysis

Values of the parameters examined and age were compared according to the *H. pylori* infection, endoscopical and histological findings by means of Mann-Whitney rank-sum test. χ^2 was used to compare qualitative variables. The diagnostic accuracy of serological parameters for identifying *H. pylori* infection was determined with receiving operating characteristic (ROC) curves; patients were subdivided as: a = true-positive, b = false-positive, c = false-negative, and d = true-negative. Sensitivity: $a/(a+c)$, specificity: $d/(b+d)$, positive predictive value: $a/(a+b)$, negative predictive value: $d/(c+d)$ and overall accuracy: $(a+d)/(a+c+b+d)$ were computed. Spearman rank correlation for comparisons between IgG-Hp, sPGL and IgG-Hp·sPGL was applied.

For all calculations, Number Cruncher Statistical Systems (NCSS Software 2000 Version, Utah, USA) software was used.

Results

Characteristics of Patients

No statistically significant differences in sex and age were found between *H. pylori*-positive and -negative children. Eighteen children were *H. pylori*-positive (40%, 10 females, mean age 10.4 ± 3 years, range 5–17) and 27 were *H. pylori*-negative (60%, 16 females, mean age 10.5 ± 3 , range 3–16). Infection was detected by all the diagnostic tests (CLO test, culture and histology) in 10 patients (55.6%), by both histology and CLO test in 6 patients (33.4%), by both endoscopy and culture in 1 patient (5.5%), and by both CLO test and culture in 1 child (5.5%).

Table 1. Endoscopic findings according to *H. pylori* infection

	<i>H. pylori</i> -positive (n = 18)	<i>H. pylori</i> -negative (n = 27)
Esophagitis	0	8
Antral nodular gastritis*	16	2
Duodenitis, superficial	1	2
Duodenitis, erosive	3	1
Antral erythema	1	5
Hemorrhagic gastritis	0	1
Normal	0	14

χ^2 test. *p < 0.05 for comparison between *H. pylori*-positive and *H. pylori*-negative patients.

The endoscopic findings of *H. pylori*-positive and -negative children are summarized in table 1. Antral nodular gastritis was significantly associated with *H. pylori*-positive patients (16 out of 18 patients, 89%) in comparison to *H. pylori*-negative ones (2 out of 27, 7%, p < 0.001).

Histopathology

All *H. pylori*-positive children had mild to moderate active chronic gastritis; 2 children also demonstrated lymphoid nodular hyperplasia. In *H. pylori*-negative patients, 25 had normal gastric mucosa, and 2 had antral chronic gastritis.

Serological Tests

Children with *H. pylori*-related gastritis had significantly both higher sPGL (12.2 ± 5.3 µg/l) levels and IgG anti-Hp antibody titers (66 ± 31 IU/l) as well as the product IgG-Hp·sPGL (865 ± 862 IU/l·µg/l) and a significantly lower sPGL/sPGL ratio (8 ± 2.3) than the *H. pylori*-negative ones (sPGL 5.8 ± 2.4 µg/l, p < 0.01; IgG-Hp 15 ± 13 IU/l, p < 0.001; IgG-Hp·sPGL 87 ± 80 IU/l·µg/l, p < 0.001; sPGL/sPGL ratio 14 ± 7 , p < 0.001). sPGL levels were also higher in *H. pylori*-positive children (91 ± 34 µg/l) than in *H. pylori*-negative children (72 ± 26 µg/l), but this finding was not statistically significant. Mean G-17 serum values were similar in *H. pylori*-positive (8.2 ± 6.5 pg/l) and *H. pylori*-negative children (8.9 ± 7 pg/l). These data are shown in figure 1.

IgG-Hp and sPGL were significantly correlated with each other (r = 0.60, p < 0.001); however, a very high positive correlation was observed between IgG-Hp and IgG-Hp·sPGL (r = 0.94, p < 0.001).

H. pylori-positive children ≥ 10 years of age (11 children, mean age 13 years) had significantly increased lev-

Fig. 1. sPGI, sPGII, sG-17, sPGI/sPGII, IgG-*Hp* and IgG-*Hp*·sPGII according to *H. pylori* infection.

Table 2. sPGI, sPGII, sPGI/sPGII, sG-17 and IgG anti-*Hp* antibodies according to *H. pylori* infection and age (over or less 10 years)

	<i>H. pylori</i> -positive (n = 18)		<i>H. pylori</i> -negative (n = 27)	
	≥10 years (n = 11)	<10 years (n = 7)	≥10 years (n = 15)	<10 years (n = 12)
sPGI, μg/l	102.3 ± 36.5 ¹	72.2 ± 21.9	69.6 ± 24.6 ¹	75.5 ± 28.5
sPGII, μg/l	13.8 ± 1.0 ¹	9.7 ± 2.5 ²	5.9 ± 2.9 ¹	5.6 ± 1.5 ²
sG-17, pg/ml	6.0 ± 3.8	11.5 ± 8.6	6.1 ± 4.5	12.4 ± 20
sPGI/sPGII	8.1 ± 2.6 ¹	7.6 ± 2.1 ²	13.9 ± 6.6 ¹	14.4 ± 7.3 ²
IgG- <i>Hp</i> , IU/l	75.9 ± 33.8 ¹	49.7 ± 18.9 ²	14.4 ± 12.6 ¹	15.5 ± 14.8 ²
IgG- <i>Hp</i> ·sPGII	1,110.5 ± 1,030.9 ^{1, 3}	478.4 ± 225.7 ^{2, 3}	93.3 ± 72.9 ¹	86.7 ± 81 ²

Mann-Whitney U test. ¹p < 0.05 for comparison between patients ≥10 years. ²p < 0.05 for comparison between patients <10 years. ³For comparison between *H. pylori*-positive patients.

els of both sPGI and sPGII and *H. pylori* antibodies as well as a significantly lower sPGI/sPGII ratio than the *H. pylori*-negative children of this age group.

In patients <10 years of age, the *H. pylori*-positive group (7 children, mean age 7.4 years) demonstrated significantly higher levels of *H. pylori* antibodies, sPGII, IgG-*Hp*·sPGII and a significantly lower sPGI/sPGII ratio than *H. pylori*-negative children (14 children, mean age 8.3 years). No significant difference was found in both sPGI and G-17.

H. pylori-positive children ≥10 years of age had a higher trend of antibody and serum pepsinogen values than positive children <10 years of age, although this finding was not statistically significant. However, among *H. pylori*-positive children, mean IgG·sPGII resulted being significantly higher in patients >10 years than in

those <10 years. Among *H. pylori*-negative children, there were no differences between children older or younger than 10 years for all the serological parameters considered. These data are summarized in table 2.

Finally, among *H. pylori*-positive patients, those with antral nodular gastritis (16 out of 18) had a higher trend of both sPGI (92.5 ± 36 μg/l) and sPGII (12.5 ± 5.7 μg/l) levels than those without this endoscopic picture (sPGI 60 ± 41 μg/l, sPGII 6.9 ± 4.8 μg/l), although without a significant difference (p = 0.39 and p = 0.12, respectively, for sPGII and sPGI). sPGI/sPGII and G-17 were similar in *H. pylori*-positive patients with (sPGI/sPGII 7.9 ± 41 μg/l and G-17 8 ± 41 μg/l) or without antral nodular gastritis (sPGI/sPGII 8.8 ± 0.31 μg/l and G-17 6 ± 4.9 μg/l, p = 0.12 and p = 0.77).

Table 3. Performance characteristics of IgG-Hp, sPGII and sPGII·IgG to discriminate for *H. pylori* infection according to the best cut-offs calculated by means of ROC curves

	Overall accuracy	Sensitivity	Specificity	PPV	NPV
IgG-Hp >30 IU/l (95% CI)	93 (84–99)	94 (75–100)	92 (73–98)	89 (68–99)	96 (77–100)
sPGII >9 µg/l (95% CI)	87 (72–94)	78 (56–94)	92 (73–98)	87 (62–97)	87 (62–97)
sPGII·IgG-Hp >241 (95% CI)	95 (84–99)	100	92 (73–98)	90 (68–99)	100

PPV = Positive predictive values; NPV = negative predictive values.

Fig. 2. Distribution of the patients according to both IgG-Hp antibodies and IgG-Hp·sPGII product levels in either *H. pylori*-positive (triangles) or *H. pylori*-negative children (circles) diagnosed by endoscopy with biopsies.

Determination of the Best Threshold of the Serological Parameters to Diagnose *H. pylori* Infection

The areas under ROC curves designed by using all possible cut-off levels to discriminate *H. pylori*-positive from *H. pylori*-negative children by means IgG anti-Hp, sPGII and IgG-Hp·sPGII were 0.96, 0.91 and 0.98, respectively. The most accurate cut-offs level for the detection of *H. pylori* infection were 30 IU/l, 9 µg/l and 241 IU/l·µg/l, respectively, for IgG-Hp, sPGII and IgG·sPGII. The performance characteristics of these cut-offs are summarized in table 3. The distribution of the patients according to IgG-Hp antibodies and IgG-Hp·sPGII levels as well as

H. pylori status is shown in figure 2. Both sPGI and G-17 had poor areas under receiving operating curves so that their best cut-offs impacted negatively either in sensitivity or specificity of the tests to diagnose *H. pylori* infection and were not reported.

Discussion

In the present study, *H. pylori* infection and gastric mucosa status, in children with upper gastrointestinal symptoms, were evaluated by means of a serological tests panel, namely sPGI, sPGII, G-17 and IgG-Hp. No child had an important gastroduodenal disease such as gastric or duodenal ulcer, or MALT lymphoma. This is in accordance with the low prevalence of endoscopic features reported in previously studies [7].

The majority of the studied *H. pylori*-positive children (16 out of 18) had the endoscopic picture of the so-called ‘antral nodular gastritis’, confirming the literature data of the association of this feature with *H. pylori* infection [45]. Among *H. pylori*-positive patients, those with antral nodular gastritis had both sPGI and sPGII levels increased in comparison to those without. Although both parameters did not reach statistically significant differences, the increase of sPGII levels was, in proportion, more important than sPGI, suggesting a potential association of the first one with this endoscopic feature which is, in turn, frequently related to a more severe *H. pylori* gastritis. However, this result needs to be confirmed with other studies, due to exiguity of the examined sample.

All the patients with *H. pylori*-negative infection had a histologically normal gastric mucosa. Conversely, *H. pylori*-positive children had non-atrophic chronic active gastritis, and 2 also presented with nodular lymphoid hyperplasia. No child resulted in being affected by intestinal metaplasia or atrophy in our cohort. The incidence of the

latter pathologic features in *H. pylori*-infected children ranges from 0 to 77.7% in recent studies [39, 41, 42]. We agree with Usta et al. [40] that the relationship between *H. pylori* infection and these lesions in children is not as strong as in adults and their development is influenced by the duration of *H. pylori* infection and environmental and genetic factors.

Very low sPGI levels associated with either low or high G-17 levels are known to be very specific serological patterns of atrophic gastritis [31, 38]; however, due to the absence of this pathologic feature in our cohort, we could not perform any type of inference.

With regard to our *H. pylori*-positive patients affected by non-atrophic chronic gastritis, both sPGI and sPGII levels increased in comparison to *H. pylori*-negative ones. However, sPGI reached a significant difference only if children >10 years were considered. Otherwise, sPGII and IgG-*Hp* levels were significantly higher in *H. pylori*-positive than in uninfected cases both in children under and over 10 years. However, age could also influence these values, indeed, *H. pylori*-positive children >10 years seem to have increased values of both sPGII and IgG-*Hp* if compared to infected younger ones, although these data were not statistically different. Young children can have an immature response or tolerance to *H. pylori*. In a Japanese study [46] of 157 children, serological determination of IgG-*Hp* was not accurate in patients <10 years of age. In the same way, Mégraud et al. [23], investigating the performance characteristics of four non-invasive tests in a cohort of 503 children (UBT, stool antigen test, and antibody detection in serum and urine), observed a trend for an improved sensitivity with increased age for all tests except the stool antigen test. For unknown reasons (probably related to a less inflammatory response in the low class of age), this behavior also seems to be the case for serum pepsinogens (especially for sPGI).

Both IgG-*Hp* and serum pepsinogen levels are influenced by the presence of *H. pylori* infection, but they follow different routes and can be considered as two different tests. IgG-*Hp* values are related to the efficacy of the immunological humoral response and are markers of exposure to the bacterium. On the other hand, increased values of both sPGII and sPGI are the consequence of *H. pylori*-induced altered gastric secretion. Intramucosal peptic activity both in antrum and corpus could be inhibited by the presence of the bacterium, determining a backflow of pepsinogens into the circulation [47, 48]. Furthermore, among *H. pylori*-positive children, those carriers of more cytotoxic *H. pylori* strains can have more increased serum pepsinogen levels [49]. Investigat-

ing the role of Cag-A and Vac-A on the serological levels of gastrin and pepsinogens in 51 *H. pylori*-positive children, Kim and Chung [33] observed a significant increase of pepsinogen levels in Cag-A-positive than Cag-A-negative children but not of gastrin. Interestingly, sPGII levels, but not sPGI, were significantly higher in patients with both Cag-A- and Vac-A-positive than both Cag-A- and Vac-A-negative ones, showing a more susceptible increase of sPGII in the presence of the most cytotoxic strains.

In our findings, with regard to *H. pylori*-positive patients, sPGII levels resulted in being proportionally higher than sPGI. A mere consequence of this matter was the significant decrease of the sPGI/sPGII ratio. The difference between sPGI and sPGII could be explained by the gastric site of constitution; the first one is produced only in the corpus glands, while the latter in both the antrum and corpus, and consequently relating to gastric inflammation independently of its localization. In our previous study, indeed, performed in 70 *H. pylori*-positive dyspeptic adult patients [35], sPGII increased significantly in comparison to *H. pylori*-negative ones and successful *H. pylori* eradication was followed by a significant reduction of both of these parameter levels and gastric mucosa neutrophilic infiltration.

Oderda et al. [32] reported increased sPGI levels in *H. pylori*-positive in comparison to *H. pylori*-negative children. However, in this work the effects of age were not considered, sPGII was not measured and sPGI was analyzed with a different method (radioimmunoassay), so it is difficult to compare this result with our data. The same authors reached by means of sPGI both 71% of sensitivity and specificity to diagnose *H. pylori* infection. Interestingly, using the combined results of sPGI and IgG-*Hp* antibodies, very good sensitivity and specificity for *H. pylori* detection (up to 95%) was reached.

In our results, both sPGI and G-17 did not have a satisfactory accuracy to diagnose *H. pylori* infection. Conversely, very good performance characteristics were achieved with both IgG-*Hp* antibodies and sPGII, after their best cut-offs (which differed from adults) were calculated. However, the combination of these two parameters in the product ameliorated the performance. In fact, IgG-*Hp*·sPGII reached both an excellent sensitivity and negative predictive value (0 false-negative). In this way, it can overcome the false-negative results related to a decreased maturity of the immune system in very young patients. If this parameter is normal, there is in fact a strong probability that patients have a healthy gastric mucosa. However, in case of positive IgG-*Hp*·sPGII, due to

the two false-positives related to this parameter, it is important to also analyze both IgG-*Hp* and sPGII levels singularly. From a practical point of view, if both sPGII and IgG-*Hp* are over the cut-off, the patients should be considered *H. pylori*-positive. In case of high sPGII but low IgG-*Hp* levels, the patients should be affected by non-*H. pylori*-related gastritis. Otherwise (high IgG-*Hp* and low sPGII levels), the patient should be previously infected and healed.

In summary, serological parameters such as sPGI and sPGII, G-17 and IgG-*Hp* could be useful as a first approach in the pediatric management of children with upper gastrointestinal symptoms. Although other non-invasive tests such as C-13 UBT or *H. pylori* stool antigen reach an excellent sensitivity [21, 28, 45] to diagnose *H. pylori* infection, the serological panel of tests could give information on various aspects of gastric mucosa, beside *H. pylori* infection. Low sPGI and either low or high G-17

could permit to exclude the presence of rare conditions such as gastric atrophy or antral gastrin cell hyperfunction [50]. On the other hand, increased sPGII levels could suggest a pattern of non-atrophic gastritis. Furthermore, the cross-combination of IgG-*Hp*•sPGII product and IgG-*Hp* antibodies can reliably diagnose or exclude the presence of *H. pylori* chronic gastritis. These non-invasive serological tests are less stressful for children if compared to endoscopy or UBT, and could be proposed in the initial management of children with upper gastrointestinal symptoms as well as in monitoring *H. pylori* eradication, if the satisfactory result observed in adults [35] will be extended in children. These results need to be confirmed in a larger cohort, also stratifying children in different age classes in order to perform the appropriate cut-off parameters before recommending their widespread clinical application as non-invasive first-pass markers of gastric disease in a pediatric population.

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