Pediatric gastritis and its impact on hematologic parameters

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Abstract

Non-invasive biomarkers, such as neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, may predict inflammation in various disorders, including gastritis, according to recent data. Nevertheless, various studies reported an association between Helicobacter pylori (H pylori) and immune thrombocytopenia in both adults and pediatric patients. The objective of our study was to evaluate the impact of pediatric gastritis, caused or not by H pylori infection on erythrocytes, their parameters, thrombocytes, mean platelet volume, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

We performed a prospective, case–control study on 151 patients aged between 1 and 17 years who presented with chronic dyspeptic symptoms. An upper digestive endoscopy with gastric biopsies and a complete blood count was performed in each case.

Control group consisted of 67 patients with normal histological findings, while the two study groups were divided into group 1—H pylori-induced gastritis (31 patients) and group 2—non-H pylori-induced gastritis (53 patients). Children from the rural area were more likely to develop both types of gastritis ($P < .01$). No significant difference was found between either of the study groups and control group in terms of platelets, mean platelet volume, NLR and PLR ($P > .05$). However, significantly higher values of lymphocytes were associated with non-H pylori-induced gastritis ($P < .01$). Comparison of the two study groups did not reflect any significant differences in terms of hematological parameters. When assessing these constants in relation to gastritis severity, severe gastritis led to a compelling decrease in hemoglobin (Hb) and hematocrit (Htc) levels. The comparison of parameters between severe, moderate, and mild gastritis did not reveal any significant results.

Childhood and adolescent gastritis does not produce a significant effect upon platelet counts, their mean volume, PLR or NLR, according to our study. An important increase in lymphocyte count might predict non-H pylori pediatric gastritis. Moreover, severe gastritis might result in an important decrease in Hb and Htc levels.

Abbreviations: H pylori = Helicobacter pylori, Hb = hemoglobin, Htc = hematocrit, LMR = lymphocyte– monocyte ratio, MCV = mean corpuscular volume, MPV = mean platelet volume, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width, SD = standard deviation.

Keywords: children, gastritis, Helicobacter pylori, hematologic parameters

1. Introduction

Chronic dyspeptic symptoms such as abdominal pain, nausea, vomiting, or bloating are often suggestive for the diagnosis of gastritis and gastropathies among pediatric patients. A prompt diagnosis of these entities might prevent life-threatening complications such as peptic ulcer disease or gastric cancer, which develops after a long-time span of chronic gastric inflammation.[1,2]

Helicobacter pylori (H pylori), one of the most frequent bacterial infection among humans, also represents the main etiologic factors of pediatric gastritis.[3–5] Several studies reported an association between this pathogen and hematologic disorders,
including immune thrombocytopenia. Recent literature data support the screening for H pylori infection in patients with idiopathic thrombocytopenic purpura, independently of the presence of gastrointestinal symptoms. An improvement of the number of platelets has been underlined after successful eradication of this bacteria. Still, this positive therapeutic response seems to be related to the pathogenicity of H pylori strains, especially the expression of CagA proteins, and therefore to the geographic variability of the infection severity. Hence, Eastern Asian populations diagnosed with thrombocytopenia were more likely proved to experience a benefic response after the eradication of H pylori infection.

In patients with H pylori positive gastritis, a useful tool for predicting a possible thrombocyte destruction is the assessment of platelet indexes. Thus, mean platelet volume (MPV) values were shown to be higher in patients diagnosed with this type of gastritis, as compared to patients without histopathological evidence of H pylori. This phenomenon might be explained by an ongoing process of platelet destruction, initially compensated by a continuous release of platelet precursor cells with an increased cellular volume into the blood flow.

Red blood cell parameters have also been evaluated in correlation with digestive disorders. Therefore, increased red blood cell volume distribution width (RDW) seems to be a predictive marker of different gastropathies, including gastric cancer, gastric ulcer, and chronic gastritis. H pylori has been shown to produce the same effect upon RDW, whereas lower values of the hematocrit (Htc), hemoglobin (Hb), and erythrocyte count have been associated with its presence in adults. However, these changes seem to be reversible after H pylori eradication, due to an improvement in serum iron and vitamin B12 levels. A special attention has been given to iron refractory iron-deficiency anemia (IRIDA) in the past years, as these changes seem to be reversible after the eradication of H pylori infection.

An abdominal ultrasound was performed for each patient, but no abnormalities were found. Moreover, in order to elucidate the etiology of the symptoms, a parasitology stool examination was recommended in every patients with complaints suggesting a parasitic infestation, such as abdominal pain, distension, flatulence, diarrhea, lack of appetite, or perianal pruritus. As functional abdominal pain and dyspepsia could have represented the cause of dyspeptic symptoms in certain cases, only patients with a family history of digestive disorders or with alarming symptoms were included in the study. Therefore, the decision of performing an upper digestive endoscopy was based upon negative abdominal ultrasound and parasitology stool examination (where applicable), positive family history of inflammatory bowel disease, celiac disease, peptic ulcer disease or H pylori infection and the presence of alarming symptoms, in accordance to the latest Rome IV criteria: dysphagia, odynophagia, persistent vomiting, hematemesis, melena, involuntary weight loss, delayed puberty, lack of appetite, symptoms persisting for more than 6 months, severe symptoms affecting daily activities, including sleep. Each patient underwent an upper digestive endoscopy with gastric biopsies (at least two samples taken from the antrum and at least two from the corpus) and a complete blood count. The upper digestive endoscopy was performed after a fasting period of at least 10 h, with each patient benefitting from a mild sedation with Diazepam, approximately 20 min prior to the procedure. All upper digestive endoscopies were performed by a single person using an Olympus gastroscope GIF P30. A microscopic examination was conducted in each case, with the help of Giemsa staining, used for identifying H pylori. The severity of gastritis was assessed in concordance with the modified, updated Sydney classification system, depending on the inflammatory modifications, activity, presence of atrophy, intestinal metaplasia and H pylori colonization, as described microscopically.

2. Materials and methods

This prospective study was conducted on a sample of 151 children aged between 1 and 17 years, who were admitted in a Pediatric Tertiary Hospital from Romania. Patients with chronic dyspeptic symptoms, such as abdominal pain, bloating, nausea, vomiting, or pyrosis were included in the study, between February 2018 and October 2019. The exclusion criteria were: patients with known chronic illnesses (including previously known hematologic disorders: immune thrombocytopenic purpura, acute lymphoblastic or myeloblastic leukemia, lymphoma, autoimmune hemolytic anemia, minor or major thalassemia), chronic medication which might alter the hematologic parameters, symptoms of other infectious diseases, parasitic infections or weight under 12 kg (due to the characteristics of the video endoscope). The subjects were divided into three groups, depending on the histopathological findings of the gastric biopsies:

1. group 1—H pylori gastritis,
2. group 2—non-H pylori gastritis, and
3. group 3—control group, consisting of patients without any pathological changes.

Laboratory tests included a complete blood count performed by an automated hematology analyzer (Cobas Integra 400 plus automated analyzer, Roche Diagnostics GmbH, Mannheim, Germany), which revealed absolute values of erythrocytes, platelets, leukocytes, and the entire leukocyte formula, as well as platelet and erythrocyte indices, including MPV, Hb, Htc, MCV, and RDW. The PLR and NLR values were calculate by dividing platelet/neutrophil count to lymphocyte count.

An abdominal ultrasound was performed for each patient, but no abnormalities were found. Moreover, in order to elucidate the etiology of the symptoms, a parasitology stool examination was recommended in every patients with complaints suggesting a parasitic infestation, such as abdominal pain, distension, flatulence, diarrhea, lack of appetite, or perianal pruritus. As functional abdominal pain and dyspepsia could have represented the cause of dyspeptic symptoms in certain cases, only patients with a family history of digestive disorders or with alarming symptoms were included in the study. Therefore, the decision of performing an upper digestive endoscopy was based upon negative abdominal ultrasound and parasitology stool examination (where applicable), positive family history of inflammatory bowel disease, celiac disease, peptic ulcer disease or H pylori infection and the presence of alarming symptoms, in accordance to the latest Rome IV criteria: dysphagia, odynophagia, persistent vomiting, hematemesis, melena, involuntary weight loss, delayed puberty, lack of appetite, symptoms persisting for more than 6 months, severe symptoms affecting daily activities, including sleep. Each patient underwent an upper digestive endoscopy with gastric biopsies (at least two samples taken from the antrum and at least two from the corpus) and a complete blood count. The upper digestive endoscopy was performed after a fasting period of at least 10 h, with each patient benefitting from a mild sedation with Diazepam, approximately 20 min prior to the procedure. All upper digestive endoscopies were performed by a single person using an Olympus gastroscope GIF P30. A microscopic examination was conducted in each case, with the help of Giemsa staining, used for identifying H pylori. The severity of gastritis was assessed in concordance with the modified, updated Sydney classification system, depending on the inflammatory modifications, activity, presence of atrophy, intestinal metaplasia and H pylori colonization, as described microscopically.
2.1. Ethics

The research was approved by the Ethics Committee of the University of Medicine, Pharmacy, Science and Technology “George Emil Palade” of Târgu Mureș (No 64/2018), respecting the principles of the declaration of Helsinki. Prior to admission in the study, one of the parents or tutors of the child had to sign an informed consent. We did not include in the study patients whose legal guardians refused the participation.

2.2. Statistical analysis

For the statistical analysis, the GraphPad Prism software was used. Descriptive statistics was helpful in calculating means and medians of age and paraclinical data of the patients. For each series of quantitative variables Shapiro–Wilk normality test was applied. Depending on its results, the comparison of means and medians was performed by applying two tests used for unpaired data: t test for values complying to a Gaussian distribution and Mann–Whitney test for values sampled from non-Gaussian distributions. The use of the later test was marked in the results tables with asterisk, whereas for the unmarked one t test was used. Chi square test was used to analyze contingency tables, for assessing the relationship between qualitative variables (sex, rural/urban background, symptoms) and the risk of developing either type of gastritis (H pylori and non-H pylori gastritis). The analysis of mean parameter differences between multiple groups was done with the help of analysis of variance (ANOVA) test. Furthermore, for multiple mean comparison parametric Bonferroni test or non-parametric Kruskal–Wallis test were used (marked with an asterisk in the result table). The significance threshold of the P-value was .05 (a confidence interval of 95%).

3. Results

3.1. Study sample design

Out of the 151 patients enrolled in the study, 67 did not present any microscopical modifications of the gastric mucosa, being included in control group, 31 were confirmed with H pylori gastritis—group 1, while 53 were histologically identified with gastritis of other etiologies—group 2 (non-steroid anti-inflammatory drug consumption, prolonged proton pump inhibitor intake, biliary reflux or formerly known H pylori infection). The following histopathological diagnoses were reported in group 2: reactive gastropathy (50.9%), focal acute gastritis (32%), and chronic, inactive gastritis (16.9%). The distribution of the study groups and subgroups was described in Figure 1. As atrophy or intestinal metaplasia were not identified in either of these cases, severity of gastritis was evaluated depending on the extent and type of cellular infiltrate of the mucosa. Therefore, intensity of lymphoplasmocytic infiltrates, amount of lymphoid aggregates (appreciative of chronic inflammation degree) and density of neutrophils were the criteria used for dividing the subjects into four subgroups in terms of severity: no pathological findings, mild, moderate, and severe gastritis. Thus, out of the 84 children diagnosed with gastritis, almost half of them (40 subjects—47.6%) suffered from a mild form, 26 (30.95%) with moderate forms and only 18 patients (21.42%) had a severe type of gastritis.
3.2. Demographic characteristics and main symptoms

The demographic characteristics of the children included in our study, as well as the distribution of the main symptoms within the study group and control groups were mentioned in Table 1. The mean age was 12.11 ± 3.22 years for the control group, 12.68 ± 3.55 years for group 1 and 11.35 ± 4.17 for group 2, without significant differences in terms of age (P = .321), or gender distribution (P = .259). However, children from rural areas (56.95%) were more likely to be diagnosed with gastritis (P < .01). The most common chronic symptoms encountered in our study indicating an upper digestive endoscopy were: abdominal pain (83.44%), nausea (27.81%), vomiting (21.85%), heartburn (14.56%), loss of appetite (5.96%), and regurgitations (1.98%), but nausea was the only symptom significantly associated with gastritis (P = .0177).

3.3. Analysis of hematological parameters

We analyzed the variations of hematological parameters between the two study groups and control group, but we also compared their values between children with H pylori and non-H pylori gastritis, in order to assess the impact of H pylori on these parameters (Tables 2 and 3). Mean platelet, leukocyte, and MPV values were higher in patients with both forms of gastritis, but did not differ significantly from the control group (P > .05). In spite of the increased lymphocyte count in both study groups compared to control group, the mean values of the lymphocytes were associated with non-H pylori gastritis (P = .007), but not with H pylori gastritis (P = .541). An increase of both PLR and NLR was noticed in H pylori induced gastritis, while a decrease of these parameters was found in children with non-H pylori gastritis, both without statistical significance (P = .904/P = .867).

### Table 1
Demographic characteristics and main symptoms of the three groups.

| Parameter                  | Helicobacter pylori gastritis (n=31) | Non-H pylori gastritis (n=53) | Control group (n=67) | P    |
|----------------------------|--------------------------------------|-------------------------------|----------------------|------|
| Age (years)                | Mean ± SD                            | 12.68 ± 3.55                 | 11.35 ± 4.17         | 12.11 ± 3.22 | .321 |
| Sex (n)                    | Female                               | 19                            | 31                   | 31    | .259 |
|                            | Male                                 | 12                            | 22                   | 36    |      |
| Background (n)             | Rural                                | 27                            | 33                   | 26    | <.001|
|                            | Urban                                | 4                             | 20                   | 41    |      |
| Abdominal pain (n)         | Yes                                  | 29                            | 44                   | 53    | .200 |
|                            | No                                   | 2                             | 9                    | 14    |      |
| Nausea (n)                 | Yes                                  | 14                            | 16                   | 12    | .017 |
|                            | No                                   | 17                            | 37                   | 55    |      |
| Vomiting (n)               | Yes                                  | 10                            | 13                   | 10    | .130 |
|                            | No                                   | 21                            | 40                   | 57    |      |
| Weight loss (n)            | Yes                                  | 1                             | 2                    | 1     | .723 |
|                            | No                                   | 30                            | 51                   | 66    |      |

n = number, SD = standard deviation.
The bold significance are used for highlighting statistically significant values (P < .05).

### Table 2
Comparison of hematologic parameters between non-Helicobacter pylori gastritis and control groups.

| Parameter                  | Non-H pylori gastritis (n=53) | Control group (n=67) | P    |
|----------------------------|-------------------------------|----------------------|------|
|                            | Mean ± SD (median)            | Mean ± SD (median)   |      |
| PLR                        | 131.9 ± 66.77 (111.4)         | 140.3 ± 53.96 (126.5)| .076 |
| NLR                        | 1.75 ± 1.212 (1.45)           | 1.96 ± 1.28 (1.68)   | .258 |
| MPV (FL)                   | 10.22 ± 1.07 (10.30)          | 9.86 ± 1.10 (10.00)  | .114 |
| Platelets (number/µL)     | 309.815 ± 94.462 (307,000)   | 301.103 ± 71.209 (294,000)| .578 |
| Leukocytes (number/µL)    | 7767 ± 2180 (7790)            | 7270 ± 1852 (6915)   | .192 |
| Neutrophils (number/µL)   | 4077 ± 1494 (3870)            | 4158 ± 1815 (5830)   | .864 |
| Lymphocytes (number/µL)   | 2751 ± 1120 (2610)            | 2268 ± 606.9 (2310)  | .007 |
| Erythrocytes (10^12/µL)   | 4.77 ± 0.422 (4.62)           | 4.86 ± 0.432 (4.86)  | .415 |
| Hb (g/dL)                  | 13.25 ± 1.17 (13.40)          | 13.46 ± 1.41 (13.50) | .460 |
| Htc %                      | 38.72 ± 3.23 (39.20)          | 39.54 ± 3.59 (39.40) | .291 |
| MCV (FL)                   | 81.27 ± 4.70 (80.50)          | 81.28 ± 3.56 (81.30) | .641 |
| RDW %                      | 13.59 ± 1.37 (13.30)          | 13.35 ± 1.59 (13.20) | .326 |

Hb = hemoglobin, Htc = hematocrit, MCV = mean cellular volume, MPV = mean platelet volume, n = number, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, SD = standard deviation.

Mann–Whitney test was used.
The bold significance are used for highlighting statistically significant values (P < .05).
Mean Hb, Htc, and MCV values were lower in the two study groups in comparison to control one (P > .05). Mean erythrocyte values were the only ones that were found to be significantly decreased in *H. pylori* gastritis group as opposed to healthy children (P = .049). In term of erythrocyte indices, RDW presented higher mean percentages in both study groups, but without statistical significance.

Table 4 describes the results of each mean comparison performed between group 1 and group 2, showing that studied complete blood count parameters and novel proposed inflammatory biomarkers, NLR, and PLR, are not influenced by the sole presence of *H. pylori* infection in the context of gastric inflammation.

### 3.4. Macroscopic findings

Assessing the endoscopic findings, we noticed that macroscopic cobblestone aspect was significantly more frequent in patients with *H. pylori* infection (P < .01). Nevertheless, other macroscopic aspects included hyperemia, edema, erosions, friability, and patchy hemorrhages. In terms of hematological parameters, no significant findings were revealed.

### 3.5. Hematological parameters and gastritis severity

Assessing the relationship between hematological parameters and gastritis severity degrees, we noticed that Hb and Htc values were significantly lower in children with severe gastritis as compared to moderate, or severe gastritis (Table 6). Nevertheless, no significant differences were found in terms of hematological parameters between children with mild, moderate, or severe gastritis (Table 6).

### 4. Discussions

Prevalence of *H. pylori* has decreased in recent years, but it still remains a public health problem in areas with a poor socioeconomic level and in individuals originating from rural environments. Our study supports these findings proving...
a positive correlation between rural area and children *H pylori*-induced gastritis. Moreover, an overall higher incidence of gastritis was found in children from rural areas.

*H pylori* infection seems to be less aggressive on children's gastric mucosa as opposed to adults, due to a boost in regulation of T cell activity, typical for this age. However, it produces a gastric mucosa as opposed to adults, due to a boost in regulation.

Leukocytes (number/mL) 7440 ± 1905 (7030)
Neutrophils (number/mL) 4033 ± 1609 (3485)
Lymphocytes (number/mL) 2318 ± 926.6 (2285)
Erythrocytes (>10⁶/µL) 4.66 ± 0.36 (4.67)
Hb (g/dL) 12.68 ± 1.43 (12.96)
Htc % 37.03 ± 4.07 (38.45)
MCV (fL) 81.96 ± 4.40 (81.00)
RDW % 13.68 ± 1.45 (13.30)

Comparison of hematologic parameters between the severe forms of gastritis and control group.

| Parameter              | Gastritis-severe form (n=18) | Control group (n=67) | P    |
|------------------------|------------------------------|----------------------|------|
| PLR                    | 144.7 ± 61.91 (121.5)        | 140.3 ± 53.96 (126.5) | .574 |
| NLR                    | 2.08 ± 1.59 (1.37)           | 1.96 ± 1.28 (1.66)   | .857 |
| MPV (fL)               | 10.21 ± 1.01 (10.00)         | 9.86 ± 1.10 (10.00)  | .330 |
| Platelets (number/µL)  | 299,833 ± 72,066 (276,000)   | 301,103 ± 71,209 (294,000) | .946 |
| Leukocytes (number/µL) | 7440 ± 1905 (7030)           | 7279 ± 224 (6940)    | .759 |
| Neutrophils (number/µL)| 4033 ± 1609 (3485)           | 4158 ± 1815 (3830)   | .814 |
| Lymphocytes (number/µL)| 2318 ± 926.6 (2285)         | 2268 ± 608.9 (2310)  | .928 |
| Erythrocytes (>10⁶/µL) | 4.66 ± 0.36 (4.67)           | 4.86 ± 0.43 (4.86)   | .080 |
| Hb (g/dL)              | 12.68 ± 1.43 (12.96)         | 13.46 ± 1.41 (13.50) | .041 |
| Htc %                  | 37.03 ± 4.07 (38.45)         | 39.54 ± 3.59 (39.40) | .023 |
| MCV (fL)               | 80.42 ± 4.88 (81.05)         | 81.28 ± 3.56 (81.30) | .401 |
| RDW %                  | 13.68 ± 1.45 (13.30)         | 13.35 ± 1.59 (13.20) | .404 |

Hb = hemoglobin, Htc = hematocrit, MCV = mean cellular volume, MPV = mean platelet volume, N = number, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, RDW = red cell distribution width, SD = standard deviation. *Mean=Whitney test was used. The bold significance are used for highlighting statistically significant values (P < .05).

Various adult studies have underlined the role of *H pylori* infection in the development of immune thrombocytopenia. Therefore, we can conclude that *H pylori* infection seems to be less aggressive on children's gastric mucosa as opposed to adults, due to a boost in regulation of T cell activity, typical for this age. However, it produces a gastric mucosa as opposed to adults, due to a boost in regulation.

Leukocytes (number/mL) 7440 ± 1905 (7030)
Neutrophils (number/mL) 4033 ± 1609 (3485)
Lymphocytes (number/mL) 2318 ± 926.6 (2285)
Erythrocytes (>10⁶/µL) 4.66 ± 0.36 (4.67)
Hb (g/dL) 12.68 ± 1.43 (12.96)
Htc % 37.03 ± 4.07 (38.45)
MCV (fL) 80.42 ± 4.88 (81.05)
RDW % 13.68 ± 1.45 (13.30)

Comparison of hematologic parameters between different grades of gastritis severity.

| Parameter              | Mild gastritis (n=40) | Moderate gastritis (n=26) | Severe gastritis (n=18) | P    |
|------------------------|-----------------------|----------------------------|-------------------------|------|
| PLR                    | 131.3 ± 61.18 (120.8) | 139.2 ± 69.79 (111.9)     | 144.7 ± 61.91 (121.5)   | .742 |
| NLR                    | 1.654 ± 0.91 (1.43)   | 2.040 ± 1.66 (1.41)       | 2.08 ± 1.59 (1.37)      | .752 |
| MPV (fL)               | 10.29 ± 0.98 (10.34)  | 9.878 ± 1.117 (9.90)      | 10.21 ± 1.01 (10.00)    | .280 |
| Platelets (number/µL)  | 301,185 ± 89,661 (298,000) | 325,577 ± 97,803 (355,500) | 299,833 ± 72,066 (276,000) | .570 |
| Leukocytes (number/µL) | 7569 ± 1788 (7715)    | 7812 ± 2613 (7320)        | 7441 ± 1005 (7030)      | .939 |
| Neutrophils (number/µL)| 3933 ± 1503 (3695)    | 4115 ± 1681 (3865)        | 4033 ± 1698 (3485)      | .921 |
| Lymphocytes (number/µL)| 2673 ± 972.8 (2549)  | 2702 ± 1772 (2670)        | 2318 ± 926.6 (2285)     | .397 |
| Erythrocytes (>10⁶/µL) | 4.77 ± 0.42 (4.80)    | 4.74 ± 0.41 (4.70)        | 4.66 ± 0.38 (4.67)      | .600 |
| Hb (g/dL)              | 13.34 ± 1.08 (13.45)  | 13.04 ± 1.75 (13.39)      | 12.68 ± 1.43 (12.95)    | .115 |
| Htc %                  | 39.04 ± 3.02 (39.54)  | 38.23 ± 4.13 (39.00)      | 37.03 ± 4.07 (38.45)    | .089 |
| MCV (fL)               | 81.96 ± 4.40 (81.00)  | 80.77 ± 7.13 (81.00)      | 80.42 ± 4.88 (81.05)    | .789 |
| RDW %                  | 13.25 ± 9.13 (13.20)  | 14.16 ± 3.24 (13.35)      | 13.68 ± 1.45 (13.30)    | .466 |

Hb = hemoglobin, Htc = hematocrit, MCV = mean cellular volume, MPV = mean platelet volume, N = number, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, RDW = red cell distribution width, SD = standard deviation. *Mean=Whitney test was used.

The bold significance are used for highlighting statistically significant values (P < .05).
reveals that the presence of mild and moderate gastritis might result in a slight increase in this hematological parameter. Contrariwise, in case of children with severe gastritis, we found a decrease in platelet count. Nevertheless, none of these results were found to be statistically significant. A possible hypothesis for these findings might be related to a compensatory mechanism expressed in the early stages of gastritis stimulating initially the production of thrombocytes. However, in patients diagnosed with \( H\text{ pylori} \) gastritis higher MPV values were found as compared to those with gastritis of other etiologies or control group, but without statistical significance.

Recent studies focused on assessing the usefulness of complete blood count parameters as a tool in gastric cancer screening.\(^{36}\) Platelets appear to be involved in promoting carcinogenesis, by increasing the secretion of pro-inflammatory cytokines.\(^{37}\) Contrariwise, lymphocyte proliferation is considered a protective factor against tumor growth.\(^{36}\) It is important to note that in our research lymphocyte counts were significantly higher in patients with non-\( H\text{ pylori} \) gastritis in comparison to healthy controls and \( H\text{ pylori} \) gastritis. As it is well known that \( H\text{ pylori} \) expresses a carcinogenic potential,\(^{38}\) lack of relevant proliferation of lymphocytes in patients from group 1 might suggest a possible long-term malignant transformation. PLR and NLR were proven to be reliable inflammatory markers for the diagnosis and staging of gastric cancer, whether used individually or in combination.\(^{39}\) In terms of \( H\text{ pylori} \) induced gastritis, the high values of these two biomarkers is caused by an increase in thrombocyte or neutrophil counts and a decrease in lymphocyte one.\(^{38,40}\) Contrariwise, our research showed an increase in mean values of PLR and NLR in children with \( H\text{ pylori}-\)induced gastritis and a decrease of these values in those with \( H\text{ pylori} \)-negative gastritis, but without statistical significance. No significant differences were noted when comparing these biomarkers or other hematologic parameters including leukocyte count between the two study groups, nor in relation with gastritis severity degrees.

The only study so far that investigated the modification of NLR values in children with \( H\text{ pylori} \) gastritis proved a mild increase of this marker in these patients as compared to control group, but without significant differences, similarly to our findings.\(^{16}\) The same study underlined a significant increase in both neutrophil and lymphocyte counts in children with \( H\text{ pylori} \) positive gastritis as opposed to ours, in which neutrophils did not differ significantly between the three groups included in our study.\(^{16}\) Furthermore, a research conducted on adult patients reported a significant association between the severity of \( H\text{ pylori} \) positive gastritis and both elevated white blood cells and NLR values explained by an increase in neutrophil count and a decrease in lymphocyte one. However, the authors underlined the reversibility of this elevated ratio after eradication therapy.\(^{40}\) Thus, multiple previously mentioned focused mainly on the impact of symptomatic or asymptomatic \( H\text{ pylori} \) infection on hematological parameters.\(^{16,38–40}\) It is important however to take into consideration that few literature data have provided reference values for these novel inflammatory markers.\(^{41}\) A recent study conducted on a large adult South Korean healthy population tried to establish reference values for NLR, PLR, MPV, and lymphocyte/monocyte ratio (LMR). These reference intervals were divided based on age and gender.\(^{42}\) Taking into account the previously mentioned reference values, we could mention that the mean values NLR, PLR, and MPV obtained in our study were similar to those reported in the study of Monzón et al, PLR and NLR values were higher in our control group. However, the authors stated that reference values for these biomarkers depend also on race and therefore further studies should be conducted in larger geographic areas.\(^{42}\)

It is well-documented that iron deficiency and vitamin B12 deficiency anemia is associated with \( H\text{ pylori} \) infection. According to a Palestinian study, this infections results in a decrease of mean erythrocytes, Hb and Htc levels, and a decrease of RDW.\(^{14}\) Moreover, eradication of the infection seems to be followed by a significant improvement in serum iron and vitamin B12 levels, even without supplementation.\(^{43}\) Nevertheless, few data describe the influence of \( H\text{ pylori} \) on erythrocytes and their indexes. Thus, the study of Li et al underlined a significant increase in RDW related to chronic gastritis.\(^{13}\) Similarly, our study revealed an association between \( H\text{ pylori} \) gastritis and lower erythrocyte values. However, hematologic parameters were not significantly different in severe forms, when compared to moderate or mild ones.

Our control group included children with no microscopic pathologic findings who were most-likely suffering from functional abdominal pain or dyspepsia taking into account the Rome IV criteria. Although Rome IV criteria does not support performing an upper digestive endoscopy in these cases, the authors of the recent guideline recognize its need in patients with alarming symptoms and the fact that this invasive maneuver cannot be avoided in all cases.\(^{20}\) Thus, according to the most recent Rome IV criteria we considered appropriate to perform an upper digestive endoscopy in these patients as well, since their symptoms or family history matched with their recommendations.

Probably one of the major limitations of this study consists in the relatively small sample size, and the reduced number of patients with \( H\text{ pylori}-\)induced gastritis. Moreover, it would have been important to assess the hematological parameters depending on different age groups, but we intend to expand our sample in the future and to accomplish this objective as well. Another potential limitation consists in the fact that the study was performed in a single medical unit, and thus we were not able to assess the role of geographic area and ethnicity on these results. Furthermore, as all of the patients included in the study presented gastro-intestinal symptoms and underwent an upper digestive endoscopy, this study did not include any asymptomatic \( H\text{ pylori} \) children, which would have constituted a valuable study group, ruling out a potential source of bias. Severity of gastritis was assessed according to the Sydney classification system, but only by taking into account inflammation and activity and not severity of \( H\text{ pylori} \) infection. As the sample of subjects with \( H\text{ pylori} \) infection was small, dividing this population into three groups and comparing each of them with patients without \( H\text{ pylori} \) infection would have led to unreliable, bias prone statistic results. Several strengths of our study are worth mentioning. Therefore, to the best of our knowledge, it is the first one that assessed the effect of childhood and adolescent \( H\text{ pylori} \) and non-\( H\text{ pylori} \) gastritis, as well as their severity on erythrocyte, platelet, lymphocyte, PLR, NLR, Hb, Htc, MCV, RDW, and MPV values. Additionally, it is among the few studies that established the diagnosis of \( H\text{ pylori} \) positive gastritis based on gastric biopsy exam since most of the findings reported in the literature were not based on upper digestive endoscopy. Further studies on larger pediatric populations, including asymptomatic \( H\text{ pylori} \) patients as well would be useful extremely useful for providing clearer conclusions, as well as the assessment of the long-term effect of \( H\text{ pylori} \) eradication upon hematological parameters.
5. Conclusions

H pylori, one of the most common infections worldwide might express a systemic impact being related to variations in hematological parameters. Our study proved that children with H pylori positive gastritis presented a mild increase in both NLR and PLR, while these markers were found to have lower values in non-H pylori gastritis. Despite the lack of statistical significance, these findings might suggest that H pylori infection might own the main role in the impairment of these parameters. Moreover, lymphocyte count might be an important predictor of non-H pylori gastritis since higher values were noticed in this group. Gastritis severity is an important trigger of anemia in pediatric patients with gastritis independently of H pylori infection taking into account that our study revealed significantly lower Hb and Htc levels in children with severe form of gastritis. Further studies are required on larger samples involving also the effect of H pylori eradication on hematological parameters in order to establish accurately the relationship between this infection and systemic inflammation, as well as long-term malignant transformation.

Author contributions

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