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Celiac disease and *H. pylori* existence in the adult population and its effects on anemia incidence

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Abstract. – OBJECTIVE: Anemia is a common extraintestinal symptom of celiac disease; however, inflammation and *Helicobacter pylori* (HP) infection can also induce anemia. Anemia is associated with both *H. pylori* infection and celiac disease, which can significantly impact public health. In our study, we aimed to determine the impact of *H. pylori* infection on anemia in celiac disease adults.

PATIENTS AND METHODS: In this study, 150 celiac disease patients with endoscopy results were retrospectively analyzed. Patients' gender, age, Oberhuber-Marsh scores, presence of *H. pylori*, presence of anemia, serum tissue transglutaminase (TTG), immunoglobulin (Ig) A and IgG levels, anti-gliadin antibody (AGA) IgA and IgG levels, Endomysial Antibody (EMA) IgA and IgG levels, serum hemoglobin, C-reactive peptide (CRP), ferritin, vitamin B12, folate, total protein, and albumin levels, serum neutrophil, monocyte, lymphocyte, eosinophil, and platelet counts, and mean corpuscular volume, mean platelet volume and platelet distribution width variables were examined. The patients were divided into HP-negative and HP-positive groups, and statistical analysis was performed between the two groups.

RESULTS: Among all patients, HP infection was seen in 24 (16%) patients. There was no difference between HP-positive and HP-negative groups in terms of gender, age, Marsh scores, serologic test levels, platelet, lymphocyte, neutrophil counts, CRP, vitamin B12, and folate levels. The anemia rate of HP-negative patients was 32.54%, HP-positive patients' rate was found to be significantly higher at 79.17% ($p<0.001$). The ferritin median of HP-negative patients was 41.49 (1-1441) and 13 (2.4-22) for HP-positive patients ($p<0.001$).

CONCLUSIONS: Anemia rates were 6.8-fold higher in HP-positive celiac patients. Celiac disease patients with anemia should have HP infection on their list of possible causes, especially in patients with refractory anemia.

Key Words:
Celiac disease, *Helicobacter pylori*, Anemia, Adult.

Introduction

Celiac disease (CD) is an autoimmune condition affecting the small intestine that has been reported in about 1% of the population[1,2]. CD is defined as an inflammatory response triggered by the body's immune system in response to gliadin components from gluten, a protein present in wheat, barley, and rye. This response causes damage to the lining of the small intestine in patients with celiac disease, and it is characterized by the infiltration of the lamina propria and the epithelium by chronic inflammatory cells and the atrophy of the villi. Both the innate and adaptive immune systems have a role in this reaction[3,4]. These histopathologic changes may lead to diarrhea, stomach discomfort, and malnutrition. Celiac disease is currently incurable; however, it may be treated with a gluten-free diet[5]. Celiac disease can present with different clinical presentations and can be diagnosed with gastrointestinal or extraintestinal symptoms or even without symptoms[6]. In patients with anemia without malabsorption findings, celiac disease can be diagnosed upon further examination.

The medical community has recognized a variety of clinical patterns of CD. Classical CD manifests with signs and symptoms of malabsorption, such as diarrhea and steatorrhea, accompanied by weight loss, anemia, or failure to thrive. But malabsorption is not a symptom of non-classical CD. This distinction is significant because certain patients with gastrointestinal symptoms and no obvious functional criteria for CD may be correctly diagnosed with CD if a physician with a high index of suspicion chooses to explore the origin of an iron deficit that no other etiology can explain[7].

The incidence of anemia varies depending on region and country. McLean et al[8] estimate

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that anemia affects around 1.62 billion people worldwide, about 25% of the world's population. Anemia is regarded as the most common extraintestinal sign of Celiac disease, and it is estimated that up to 20-30% of patients with celiac disease are anemic[9-11]. Some studies[12,13] have even reported iron deficiency anemia rates of up to 85%. The resulting atrophy of the duodenal mucosa is thought to be responsible for malabsorption and numerous micronutrient and mineral deficiencies, including folate, vitamin B12, and vitamin D, may contribute to the development of anemia[14]. Even though anemia is a common symptom of celiac disease, nutritional deficiencies alone do not explain this phenomenon in all cases, and inflammation appears to contribute, as evidenced by the presence of anemia of chronic disease in some individuals[15].

Helicobacter pylori (*H. pylori*) infection can also cause anemia. It is one of the most common bacterial infections worldwide and is estimated to affect about half the world's population[16,17]. *H. pylori* can cause a variety of stomach and intestinal symptoms, such as abdominal pain, nausea, bloating, and heartburn[17]. *H. pylori* infection causes chronic inflammation in the stomach and small intestine, which can lead to bleeding in the gastrointestinal tract. This bleeding can be subtle, therefore, may go unnoticed but can cause chronic blood loss and malabsorption, leading to anemia. Anemia caused by *H. pylori* infection is typically microcytic anemia, characterized by small red blood cells, low hemoglobin levels, and low iron levels in the blood[17].

Recent studies[18] have shown that *H. pylori* infection and celiac disease are associated with each other and with anemia. The multifactorial process by which *H. pylori* and celiac disease induce anemia comprises malabsorption of nutrients, persistent inflammation, and blood loss[19]. Because anemia is a non-specific symptom that may be caused by various illnesses, the diagnosis of celiac disease and *H. pylori* infection is sometimes delayed or ignored[20].

Celiac disease and *H. pylori* infection significantly impact public health and healthcare resources. They can cause a wide range of symptoms and complications, and they can have a significant impact on a person's quality of life[21]. Both can cause malnutrition, duodenitis, cramping sensations, increased risk of certain types of cancer, and anemia if left undiagnosed and untreated[17,22]. The only treatment for celiac disease is a gluten-free diet, which can be difficult and expensive. Therefore, patients and clinicians must understand these diseases to manage similar symptoms, outcomes, and accompanying complications effectively.

In our study, we aimed to see the effect of *H. pylori* infection on anemia incidence in adult celiac disease patients.

Patients and Methods

This study was planned as a retrospective study and approved by the Hitit University Faculty of Medicine Clinical Researches Ethics Committee (Date: 16.03.2023, Decision No.: 2023-32). All procedures were carried out following the ethical rules and the principles of the Declaration of Helsinki. All celiac disease patients with a histopathology report confirming the diagnosis between January 2015 and January 2022, were screened retrospectively, and 179 patients were found. Patients under the age of 18, patients with a known hematological disease, patients who are using drugs that could affect hematologic parameters (such as steroids, chemotherapeutic agents, and antibiotics), patients with acquired immune deficiency syndrome (AIDS), pregnancy, or breastfeeding status, and those whose blood results before the initiation of treatment could not be obtained were excluded from the study. Twenty-nine patients were excluded, and 150 celiac disease patients were included in the study. Gender, age, Oberhuber-Marsh scores, presence of anemia, serum tissue transglutaminase (TTG) immunoglobulin (Ig) A and IgG levels, anti-gliadin antibody (AGA) IgA and IgG levels, endomysial antibody (EMA) IgA and IgG levels, serum hemoglobin, C-reactive peptide (CRP), ferritin, vitamin B12, folate, total protein, and albumin levels, serum neutrophil, monocyte, lymphocyte, eosinophil and platelet counts, and mean corpuscular volume (MCV), mean platelet volume (MPV), platelet distribution width (PDW) values of 150 patients, and the *H. pylori* infection status of the patients were obtained from the archive system retrospectively. Patients were divided into two groups according to *H. pylori* infection. TTG IgA and IgG, AGA IgA and IgG cut-off for positive immunoglobulin test was chosen as 10 IU/mL, EMA IgA and IgG cut-off was chosen as 20 IU/L. According to World Health Organization's guidelines (https://apps.who.int/iris/bitstream/handle/10665/85839/

WHO_NMH_NHD_MNM_11.1_eng.pdf), the anemia threshold was designated as 12 mg/dL for women and 13.5 mg/dL for men.

Statistical Analysis

For statistical analysis, SPSS Statistics for Windows software was used (Version 26; IBM Corp., Armonk, NY, USA). Descriptive statistics were reported using numbers and percentages for categorical variables. Numerical variables were reported as mean ± standard deviation for normally distributed data and median and minimum and maximum values in parentheses for non-parametric distribution. Data distribution was evaluated using the Shapiro-Wilks test. Using Pearson and Spearman correlation coefficients, relationships between variables were analyzed. Distribution-based analysis was used to compare the numerical measures of two separate study groups. Serum hemoglobin level and monocyte count were assessed using Student *t*-test. Age, immunological blood markers, MCV, MPV, PDW, serum neutrophil, monocyte, lymphocyte, eosinophil, platelet counts, CRP, ferritin, vitamin B12, folate, total protein, and albumin levels were evaluated with the Mann-Whitney U test. The Chi-Square test was used to evaluate the statistical significance of categorical variable differences across groups. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for risk analysis. For the statistical significance level, $p<0.05$ was accepted as meaningful.

Results

There were 116 female patients (77.33%) and 34 male patients (22.67%) in the group. The median age of the patients was 34 (18-80) years. Most of the patients' Oberhuber-Marsh class were 3b (39.33%), closely followed by classes 3a (22.67%) and 3c (20%). All patients' data are presented in Table I. TTG IgA was the most frequently seen immune marker, with a 77.33% positivity rate. EMA IgG was reported as negative in the majority of the patients (85.33%) (Table II).

The mean hemoglobin level was 12.69±1.91 mg/dL, and the median MCV was 84.05 (58.9-108) fL/oz. The median ferritin level was 22.8 (1-1,441), vitamin B12 level was 291.5 (107-1438), and folate level was 6.6 (0.5-20). *H. pylori* infection was found in 16% of the patients, and 60 of 150 patients (40%) were anemic.

Comparison Between H. pylori-Negative and H. pylori-Positive Groups

Patients were divided into two groups based on their *H. pylori* infection status. Regarding gender and age distribution, the two groups were similar ($p=0.792$ and $p=0.931$, respectively). There was no histopathological difference between the groups ($p=0.558$). No significant differences were found between immunological marker levels (Table I).

When hematologic parameters were investigated, platelet count, lymphocyte count, MPV, PDW, monocyte count, neutrophil count, and eosinophil count levels were similar between HP-negative and positive groups ($p=0.523$, $p=0.104$, $p=0.220$, $p=0.297$, $p=0.386$, $p=0.929$, $p=0.784$, and $p=0.107$, respectively). HP-positive patients' mean hemoglobin levels were significantly lower than HP-negative patients' hemoglobin levels (11.94±1.3 *vs.* 12.84±1.98, $p=0.034$). In the HP-positive group, MCV was also lower than in the HP-negative group, with a median of 78.95 against a median of 84.55 ($p=0.048$). At the same time, the rate of anemia is 32.54% in HP-negative patients, significantly increasing to 79.17% in HP-positive patients ($p<0.001$). HP-positive celiac disease patients had a 6.8-fold greater risk of anemia than HP-negative CD patients (OR 7.878, 95% CI 2.748-22.586, $p<0.001$).

C-reactive peptide, total protein, and albumin levels were similar between the two groups ($p=0.107$, $p=0.965$, $p=0.508$, respectively). In HP-negative patients, the mean of ferritin was 41.49 (1-1,441), but in HP-positive patients, ferritin levels were significantly lower, with a median of 13 (2.4-22) ($p<0.001$). There were no statistically significant differences in vitamin B12 and folate levels between HP-positive and HP-negative groups.

The relations between Oberhuber Marsh classifications and immunologic parameters are presented in detail in Table III and Figure 1. TTG IgG and EMA IgG were statistically significantly different between Oberhuber-Marsh classes ($p<0.001$ for both). Both immunologic markers were found to be highest in the Oberhuber-Marsh class 3b. Ferritin, folate, and vitamin B12 levels were not statistically different between histopathologic classes ($p=0.708$, $p=0.194$, $p=0.433$).

Discussion

Celiac disease, H*elicobacter pylori*, and anemia are all health conditions that have been

Table I. Data of all patients and comparison between *H. Pylori* groups.

Variables		All patients (n=150)	HP Negative (n=126)	HP Positive (n=24)	Statistical Significance
Gender	Male	34 (22.67%)	28 (22.22%)	6 (25%)	0.792
	Female	116 (77.33%)	98 (77.78%)	18 (75%)	
Age		34 (18-80)	34 (18-80)	36 (18-79)	0.931
Anemia	Normal	90 (60%)	85 (67.46%)	5 (20.83%)	<0.001
	Anemic	60 (40%)	41 (32.54%)	19 (79.17%)	
Marsh	1	12 (8%)	9 (7.14%)	3 (12.5%)	0.558
	2	8 (5.33%)	8 (6.35%)	0 (0%)	
	3a	34 (22.67%)	29 (23.02%)	5 (20.83%)	
	3b	59 (39.33%)	48 (38.1%)	11 (45.83%)	
	3c	30 (20%)	25 (19.84%)	5 (20.83%)	
	4	7 (4.67%)	7 (5.56%)	0 (0%)	
TTG IgA		74.6 (0.17-304.23)	81.38 (0.17-304.23)	65.35 (0.45-226)	0.214
TTG IgG		5.73 (0.23-228.12)	5.68 (0.23-228.12)	5.78 (0.86-151.12)	0.749
AGA IgA		20.58 (0.44-309.52)	21.1 (1.35-303.64)	11.94 (0.44-309.52)	0.400
AGA IgG		21.31 (0.95-301.94)	20.74 (0.95-301.2)	24.69 (2.64-301.94)	0.464
EMA IgA		38.5 (0.6-309.04)	40.7 (0.92-309.04)	26.95 (0.6-302.1)	0.222
EMA IgG		4.37 (0.04-134)	4.62 (0.04-134)	4.12 (1.48-123)	0.975
Hemoglobin		12.69±1.91	12.84±1.98	11.94±1.3	0.034
MCV		84.05 (58.9-108)	84.55 (58.9-108)	78.95 (59-95.2)	0.048
Platelet count		287.5 (64-742)	282 (102-742)	307.5 (64-580)	0.523
Lymphocyte count		2.03 (0.63-4.59)	1.97 (0.63-4.59)	2.1 (0.75-4.18)	0.104
MPV		9.85 (6.8-12.6)	9.95 (6.8-12.5)	9.5 (7.9-12.6)	0.220
PDW		15.3 (8.9-16.8)	15.3 (8.9-16.5)	15.65 (9.4-16.8)	0.297
Monocyte count		0.43±0.14	0.43±0.14	0.46±0.17	0.386
Neutrophil count		3.76 (1.4-11.43)	3.7 (1.4-11.43)	3.81 (1.41-6.15)	0.929
Eosinophil count		0.13 (0.01-0.79)	0.13 (0.01-0.79)	0.13 (0.02-0.41)	0.784
CRP		3.2 (3-10.8)	3.2 (3-10.8)	3.13 (3-10)	0.107
Ferritin		22.8 (1-1,441)	41.49 (1-1,441)	13 (2.4-22)	<0.001
Vitamin B12		291.5 (107-1,438)	294.85 (107-1,438)	276 (144-983)	0.951
Folate		6.6 (0.5-20)	6.72 (0.5-20)	5.8 (0.6-10.06)	0.264
Total Protein		7.29 (2.9-8.9)	7.29 (2.9-8.57)	7.25 (6-8.9)	0.965
Albumin		4.3 (3.1-7.4)	4.3 (3.1-7.4)	4.35 (3.6-5)	0.508

HP: *Helicobacter pylori*, TTG: Tissue transglutaminase, AGA: Anti-gliadin antibody, EMA: Endomysial antibody, MCV: mean corpuscular volume, MPV: mean platelet volume, PDW: platelet distribution width, CRP: C-reactive peptide.

Table II. Immunologic marker positivity of all patients.

Immunologic markers		All patients
TTG IgA	Negative	34 (22.67%)
	Positive	116 (77.33%)
TTG IgG	Negative	86 (57.33%)
	Positive	64 (42.67%)
AGA IgA	Negative	55 (36.67%)
	Positive	95 (63.33%)
AGA IgG	Negative	46 (30.67%)
	Positive	104 (69.33%)
EMA IgA	Negative	51 (34%)
	Positive	99 (66%)
EMA IgG	Negative	128 (85.33%)
	Positive	22 (14.67%)

TTG: Tissue transglutaminase, AGA: Anti-gliadin antibody, EMA: Endomysial antibody, IgG: Immunoglobulin G, IgA: Immunoglobulin A.

extensively studied in the medical literature and have been linked to each other in various studies. This research aimed to find the frequency of anemia and its relationship to *H. pylori* infection among adult celiac patients.

Celiac disease can occur at any age, from infancy to old age, and is most commonly diagnosed in individuals between 30 and 60 years of age, although it can be diagnosed at any age[23]. In our study, the median age of diagnosis was 34 years, which was consistent with existing literature, and also did not differ between HP-negative and HP-positive patients. Some studies[24,25] have reported that celiac disease is more common in females, with a female-to-male ratio of about 2:1 or 3:1. This ratio was slightly higher in our population, around 3.4 to 1.

Table III. Immunologic and hematologic marker medians of Oberhuber-Marsh stages.

Variables	Oberhuber-marsh stage						Statistical significance
	Marsh 1	Marsh 2	Marsh 3a	Marsh 3b	Marsh 3c	Marsh 4	
TTG IgA	37.78 (0.45-218.56)	78.32 (1.77-296.2)	76.59 (0.17-278)	71 (0.84-304.23)	83.19 (0.65-303.3)	210.88 (1.07-213.63)	0.401
TTG IgG	0.88 (0.35-15.59)	2.97 (0.99-32)	3.57 (0.23-112)	11.9 (0.8-200)	23.45 (0.6-228.12)	2.07 (1.24-228)	< 0.001
AGA IgA	7.97 (1.45-209.29)	28.75 (2.34-54.94)	23.09 (1.69-208.6)	12.26 (0.44-203.68)	24.23 (1.59-309.52)	71.64 (52-112.11)	0.014
AGA IgG	8.84 (0.95-301.32)	12.16 (1.49-98.62)	20.29 (2.05-290.1)	23.42 (1.49-234.9)	25.06 (2.64-301.94)	25.85 (13.02-107.89)	0.242
EMA IgA	12.9 (1.42-88)	57.25 (1.62-205.1)	39.17 (0.92-116)	29.8 (1.1-189)	85.15 (0.6-309.04)	185 (9.15-300.58)	0.001
EMA IgG	2.28 (0.85-24.1)	3.71 (2.09-19.1)	3.09 (0.97-134)	6.17 (2.65-64.4)	12.8 (0.04-123)	2.53 (2.25-10.9)	< 0.001
CRP	3.13 (3-5.46)	3.12 (3-5.93)	3.25 (3-10)	3.2 (3-6.9)	3.17 (3-10.8)	3.2 (3-4.57)	0.832
Ferritin	38.69 (5.5-75)	14.3 (6.99-50)	39.33 (2.96-886)	20.31 (2.2-1441)	20.37 (1-145)	17.6 (2.9-90)	0.708
Vitamin B12	360 (121-1438)	319 (204-843)	296.85 (107-724)	269 (124-707)	282.5 (117-729)	310 (201-563.6)	0.433
Folate	8.61 (2.2-17.19)	8.67 (5.3-14)	7.03 (1-19)	6 (0.5-20)	6.1 (0.6-16)	6 (0.9-8.92)	0.194

TTG: Tissue transglutaminase, AGA: Anti-gliadin antibody, EMA: Endomysial antibody, IgG: Immunoglobulin G, IgA: Immunoglobulin A, CRP: C-reactive peptide.

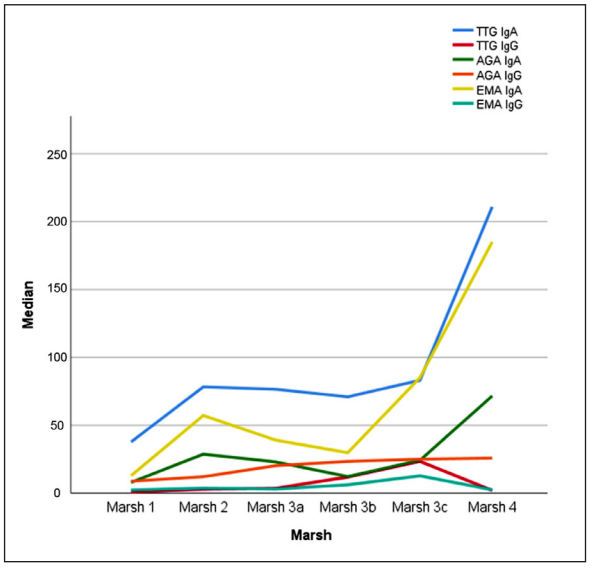

Figure 1. Line graph of serologic test levels and Marsh classes. TTG: Tissue transglutaminase, AGA: Anti-gliadin antibody, EMA: Endomysial antibody, IgG: Immunoglobulin G, IgA: Immunoglobulin A.

A diagnosis of CD requires intestinal biopsy and histological evaluation[26]. Some studies[27,28] have reported a correlation between the degree of anemia, the severity of villous atrophy, and the degree of intestinal inflammation in the small intestine mucosa in celiac disease patients, as determined by the modified Marsh classification. Another study published by Berry et al[29] found that anemia was more common and severe in celiac patients with higher grades of mucosal damage. Similar to previous publications[27,28], the majority of patients were classified as modified Marsh-Oberhuber stage 3b in our study, but contrary to other studies' results[29], there were no major histopathological differences between anemic and normal patients.

In our study, we discovered that 16% (24 patients) of CD patients were infected with HP. This rate is considerably higher than that observed in a recent study[30] of the pediatric CD population. Jozefczuk et al[30] found a rate of 5.4% among children aged 3 to 12 with celiac disease. However, a more recent study by Kovacheva-Slavova et al[31] found that the prevalence of HP in the general adult population is 48%, which is higher than our findings.

The diagnosis and ongoing management of celiac disease may be assisted by serologic testing[32]. In our study, we could not observe any significant difference between HP-positive and negative groups regarding serologic tests. Nevertheless, as expected, we observed statistically significant differences between serologic tests and Oberhuber-Marsh classes. Similar to our study results, Mansour et al[33] found that Marsh-Oberhuber type 3b and 3c correlated with increased seropositivity.

One study[34] found that 42% of patients with CD were *H. pylori* positive and that *H. pylori* play a vital role in the development of iron deficiency anemia in celiac disease. However, there are findings[35] contrary to the results of this study; another study[35] showed that the frequency of *H. pylori* infection was not significantly different between celiac patients with and without iron deficiency anemia. In our study, 32.54% of *H. pylori*-negative patients and 79.17% of *H. pylori*-positive patients were anemic, and HP-positive celiac disease patients had a 6.8-fold greater risk of anemia than HP-negative CD patients. However, no statistically significant difference between *H. pylori*-positive and negative groups regarding vitamin B12 and folic acid levels and Oberhuber-Marsh classification was found in our study. This suggests that in addition to malnutrition and inflammation, anemia (especially iron deficiency anemia) may be caused by another pathway. Increased hepatocyte hepcidin production in response to IL-6 production secondary to inflammatory conditions such as *H. pylori* infection, inflammatory bowel disease, and celiac disease leads to decreased iron absorption[36]. Even though we could not show any significant histopathological differences in mucosal inflammation between anemic and normal patients, this systemic hepcidin response could be the reason for low ferritin levels and higher anemia rates in *H. pylori*-positive patients in our study.

The causes of anemia in celiac disease are multifactorial and still under investigation. We think that our study will be helpful in terms of evaluating the relationship between *Helicobacter pylori* and anemia in celiac patients.

This study has limitations since it is a retrospective, single-center investigation. Among these are the inherent restrictions of a retrospective design and reliance on medical records, as well as the study's limited generalizability due to its single-center setting. While the study provides valuable insights, further research is needed to validate and expand upon these findings using larger, prospective studies with a wider range of variables considered.

Conclusions

Our study shows the connection between *Helicobacter pylori* and higher rates of anemia in celiac disease patients. It should be taken into consideration that the incidence of anemia is increased in celiac patients with HP infection. When anemia is detected in celiac disease, HP infection should be considered as one of the underlying causes, in addition to malnutrition, villus atrophy, and chronic inflammation. Especially diet-compliant celiac patients with refractory anemia should be evaluated for HP eradication.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The study was carried out with the permission of the Hitit University Faculty of Medicine Clinical Researches Ethics Committee (Date: 16.03.2023, Decision No.: 2023-32).

Informed Consent

Because of the retrospective design of this study, no written informed consent form was obtained from patients.

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Authors' Contribution

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Data Availability

The authors indicate that data are available upon request to the corresponding author.

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