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RESEARCH ARTICLE

Predictors of anemia without active bleeding signs in patients referred for endoscopy

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Objective: The objective of the present study is to clarify the value of clinic, endoscopic, and histologic variables that may predict anemia in patients performing esophagogastroduodenoscopy for gastrointestinal complaints in the absence of bleeding signs or lower digestive disease. **Methods**: This study included 654 patients referred for endoscopy that were divided based on biological parameters performed in the same day in the study group (306 patients diagnosed with anemia) and the control group (348 patients without anemia). **Results**: Anemia is frequent in elderly patients, especially in the presence of premalignant gastric lesions, and it is associated with multiple comorbidities. In two multivariate regression models antivitamin K oral anticoagulants were found to be independently associated with anemia (p = 0.01), but not with antiplatelet therapy, or with non-antivitamin K anticoagulants. Multiple regression models support that epigastric pain and heartburn are inversely associated with anemia, while weight loss remained an independent predictor for simultaneous anemia and premalignant lesions. Non-infectious chronic gastritis (p<0.001) is an independent predictor for anemia and premalignant gastric lesions, increasing the odds of anemia by 2.2 times, while reactive gastropathy is inversely associated. Gastric erosions and ulcer remained independent predictors for concomitant anemia and premalignant lesions. **Conclusions**: Chronic inactive gastritis and premalignant gastric histologic lesions are predictors for anemia in endoscopic population, while active H. pylori infection is not. Dyspeptic symptoms, epigastric pain (p<0.001,OR 0.2-0.5) and heartburn (p<0.001,OR 0.07-0.3) are inversely associated with anemia alone or associated with premalignant gastric lesions.

Keywords: anemia, chronic gastritis, dyspepsia, Helicobacter pylori, premalignant gastric lesions

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Introduction

Anemia, which affects both developing and developed nations, is a significant public health issue that has a serious economic impact, especially in low and low-middle-income countries [1].

Due to the frequent manifestation of anemia in gastrointestinal (GI) tract diseases, patients are often referred to gastroenterologists. Nowadays, esophagogastroduodenoscopy (EGD), enteroscopy, and colonoscopy are key components of the anemia diagnostic pathway [2]. Functional dyspepsia (FD) is represented by the presence of epigastric pain or burning sensation, early satiation, or postprandial fullness that have started at least 6 months before diagnosis with no evidence of structural disease. Known risk factors linked to dyspepsia are female gender, use of gastrotoxic medication (e.g., non-steroidal anti-inflammatory drugs) [3], and *Helicobacter pylori (H. pylori)* infection with modest evidence [4].

Anemia is considered a consequence of *H. pylori* infection, and the prevalence of anemia is higher in *H. pylori* positive subjects (especially in women) [5]. Iron deficiency anemia (IDA) is the most prevalent type of anemia in gastroenterological diseases. The function that *H. pylori* played in the appearance of IDA has not been completely clarified [6]. Chronic *H. pylori* infection can lead to IDA through blood loss, iron consumption, or malabsorption. Various other processes could contribute to anemia in *H. pylori*-infected patients, including iron sequestration leading to inhibition of iron transporter molecules expression that results in free iron absorption inhibition and cobalamin malabsorption [5].

Atrophic gastritis (AG) and gastric intestinal metaplasia (IM) are the conditions that confer an increased risk of developing gastric adenocarcinoma [7]. *H. pylori*-induced inflammation leads to mucosal damage, and it is associated with gastric cancer in more than 90% of cases [8].

Even though prompt endoscopy is not indicated for most patients with dyspepsia [3], subclinical anemia and lack of symptoms in case of AG should be taken into consideration when recommendations are made.

Our study aims to clarify the value of clinic, endoscopic, and histologic variables that may predict anemia, irrespective of its type in patients performing EGD for gastrointestinal complaints in the absence of bleeding signs or diseases of the lower gastrointestinal tract.

Methods

Selection of patients

This single-center study, conducted in the Medical Clinic of Emergency County Hospital, Târgu Mures, Romania,

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enrolled consecutive patients who underwent esophagogastroduodenoscopy (EGD) and usual blood tests between January 2016 and February 2022. The patients who were included in the study were referred for endoscopy due to dyspeptic symptoms (epigastric pain or burning sensation, early satiation, postprandial fullness, nausea, vomiting, abdominal meteorism), loss of appetite, and unexplained weight loss. A modified version of the Leeds Dyspepsia Questionnaire was used to evaluate the frequency and severity of dyspeptic symptoms. [9] The study included 306 patients with anemia, irrespective of its type based on hemoglobin levels under 12g/dL in women and under 14g/dl in men. These cut-off values were proposed in accordance with the reference ranges used by the laboratory of Târgu Mureș Emergency County Hospital, Romania. The mean corpuscular volume (MCV range taken into consideration as normal) was 80-100 fL, and the reference range for serum iron is 55–160 µmol/L. No data regarding CRP or ferritin values were included in our study.

All patients with anemia performed a colonoscopy, and they were included in the study if not pathological findings were revealed. The control group included 348 patients without anemia. Exclusion criteria were: acute/active bleeding symptoms or endoscopic findings, positive fecal occult blood test, previous *H. pylori* eradication therapy, celiac disease, cancer diagnosis irrespective of localization, missing data referring to drug consumption, social behavior or gastric biopsies. All patients with anemia performed a colonoscopy, and they were included in the study if no significant pathological findings and bleeding marks/signs (e.g. complicated hemorrhoids, large colonic polyps, diverticular disease, tumor, arteriovenous malformation, colitis)

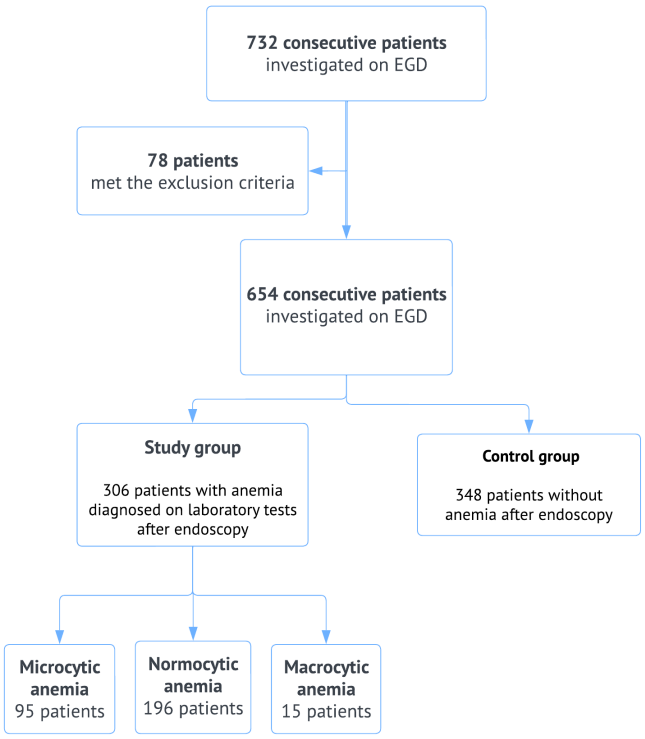

Fig. 1. The selection of patients

or were revealed". This study was approved by the Medical Ethics Committee for the Clinical Study of Medicines of the County Emergency Clinical Hospital Târgu Mureș, decision number nr. 27576/10.11.2021, and a written consent was obtained from every patient involved.

Data collection

Data regarding chronic medications with drugs that impact gastric mucosa were reviewed: non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants (antivitamin K anticoagulants and non-antivitamin K oral anticoagulants), and antiplatelet drugs (clopidogrel, ticagrelor, low-dose aspirin) were considered if used at least 30 days before performing the examination. Direct interviews and medical records were both used to gather information regarding drug use.

Recorded comorbidities were: respiratory diseases (chronic obstructive pulmonary disease, pulmonary fibrosis, or asthma), cardiovascular conditions (ischemic heart disease, valvulopathies, and congestive heart failure), cerebrovascular diseases (ischemic and hemorrhagic stroke), chronic kidney disase (CKD), chronic osteoarticular diseases and diabetes mellitus.

Endoscopic and Histologic Data

During the endoscopic examination, gastric erosions and ulcer were noted. According to Sydney's protocol, five biopsies were obtained: two from the antrum, two from the corpus (the greater and lesser curvature), and one from the angular notch, sent in three different containers, one for each biopsy site. Duodenal biopsies were taken in selected cases, but patients with celiac disease were excluded[10].

The classification and grading of gastritis were performed according to the Updated Sydney System protocol. Hematoxylin and Eosin (H&E), modified Giemsa, and PAS-alcian blue were used to color each gastric and duodenal biopsy. Reactive gastropathy was considered in the presence of foveolar hyperplasia, mucin depletion in foveolar cells, replacement of the lamina propria with fibromuscular tissue, and/or capillary congestion. *H. pylori* gastritis was defined when the bacteria was observed in at least one biopsy using H&E and Giemsa stain. Immunohistochemistry was performed in patients with persistent inflammation and PPI therapy in selected cases using FLEX polyclonal rabbit anti-*H. pylori* antibody, Ready to Use (DakoAutostainer)[11].

Non-infectious chronic gastritis was considered in patients with chronic mucosal changes, vascular ectasia, lamina propria fibrosis, and variable grades and types of inflammatory cell infiltration (plasma cells, lymphocytes, and/or neutrophils), in the absence of *H. pylori* infection, or previous eradication therapy, or other documented infections. Atrophic gastritis (AG) and intestinal metaplasia (IM) were defined together as premalignant gastric lesions [12].

Statistical Analysis

Categorical variables are expressed as absolute values and percentages. Continuous variables presented a non-normal distribution. Categorical data was compared using Fischer's exact test. Statistically significant variables ($p < 0.05$) and factors related to the pathophysiological mechanism of anemia were included in the univariate and multiple regression analysis, to identify independent predictors of anemia. All tests used in this research were two-sided. A p-value <0.05 was considered statistically significant. All data were computed using Graphpad Prism 8.0.2 Software.

Results

The study included 48.2% male patients and 51.8% female patients. Anemic patients, irrespective of the type, were significantly older than controls (p<0.001) and presented more often with cardiovascular diseases (p<0.001), arterial hypertension (p=0.02), chronic respiratory disease (p=0.008), diabetes mellitus (p=0.0001), and chronic kidney disease (p<0.001). No association was found between anemia and cerebrovascular, liver, and osteoarticular diseases. Non-antivitamin K oral anticoagulants (p<0.001), antivitamin K anticoagulants (p=0.03), and antiplatelet drugs (p = 0.03) consumption were statistically significantly associated with anemia, but not NSAIDs consumption (Table 1).

Epigastric pain (p<0.001), heartburn (p<0.001), nausea/vomiting (p=0.004), and bloating (p=0.001) were more frequent in the control group. However, loss of appetite (p=0.04) and weight loss (p=0.02) were statistically significantly associated with anemia.

Gastric erosions and gastric ulcer were present more frequently in patients with anemia (p<0.001). Anemia was statistically associated with non-infectious chronic gastritis (p<0.001), intestinal metaplasia (p=0.007), and glandular atrophy (p=0.0002). No association was found between anemia and reactive gastropathy, *H. pylori* gastritis, or duodenitis (Table 1).

Endoscopic lesions (gastric erosions and ulcer) remained independent predictors for anemia even in multivariate logistic regression analysis (all p<0.05). The presence of non-infectious chronic gastritis increased the odds of de-

Table 1. Group differences regarding demographic, clinical, endoscopic and histological features in anemic and non-anemic patients

Parameter	Total N=654	Patients with anemia N=306	Non-anemic patients N=348	p-value	OR	95% CI
	n(%)	n(%)	n (%)			
Age > 65 years	315 (48.1)	189 (61.7)	126 (36.2)	**<0.001**	2.8	2.0-3.9
Comorbidities						
Cardiovascular diseases	356 (54.4)	204 (66.6)	152 (43.6)	**<0.001**	2.5	1.8-3.5
Cerebrovascular diseases	40 (6.1)	24 (7.84)	16 (4.59)	0.1	1.7	0.9-3.4
Chronic respiratory diseases	81 (12.3)	49 (16.01)	32 (9.1)	**0.008**	1.8	1.1-2.9
Diabetes mellitus	116 (17.7)	74 (24.1)	42 (12)	**0.01**	2.3	1.5-3.5
Arterial hypertension	381 (58.2)	193 (63)	188 (54)	**0.02**	1.4	1.0-1.9
Liver diseases	127 (19.4)	58 (18.9)	69 (19.8)	0.8	0.9	0.6-1.3
Osteoarticular disorders	106 (16.2)	46 (15)	60 (17.2)	0.4	0.8	0.5-1.2
Chronic kidney disease	89 (13.6)	69 (22.5)	20 (5.7)	**<0.001**	4.7	2.8-8.1
Drug consumption						
Antiplatelet drugs	208 (31.8)	110 (35.9)	98 (28.1)	**0.03**	1.4	1.0-1.9
Non-antivitamin K oral anticoagulants	62 (9.48)	45 (14.7)	17 (4.8)	**<0.001**	3.3	1.9-5.9
Antivitamin K oral anticoagulants	46 (7.03)	29 (9.47)	17 (4.8)	**0.03**	2.0	1.0-3.7
NSAIDs	109 (16.6)	43 (14)	66 (18.9)	0.1	0.6	0.4-1.0
PPIs	386 (59)	191 (62.4)	195 (56)	0.1	1.3	0.9-1.7
Symptoms						
Epigastric pain	289 (44.1)	91 (29.7)	198 (56.8)	**<0.001**	0.3	0.2-0.4
Heartburn	135 (20.6)	21 (6.8)	114 (32.7)	**<0.001**	0.1	0.09-0.2
Regurgitation	23 (3.51)	8 (2.6)	15 (4.3)	0.2	0.5	0.2-1.3
Nausea/Vomiting	130 (19.8)	46 (15)	84 (24.1)	**0.004**	0.5	0.3-0.8
Bloating	115 (17.5)	38 (12.4)	77 (22.1)	**0.001**	0.4	0.3-0.7
Early satiety	6 (0.91)	3 (0.9)	3 (0.8)	0.9	1.1	0.2-4.9
Loss of appetite	82 (12.5)	47 (15.3)	35 (10)	**0.04**	1.6	1.0-2.6
Diarrhea	37 (5.65)	13 (4.2)	24(6.8)	0.1	0.5	0.2-1.2
Weight loss	88 (13.4)	51 (16.6)	37 (10.6)	**0.02**	1.6	1.0-2.6
Endoscopic and histologic findings						
Gastric erosions	160 (24.4)	111 (36.2)	49 (14)	**<0.001**	3.4	2.3-5.0
Gastric ulcer	118 (18)	100 (32.6)	18 (5.1)	**<0.001**	8.9	5.3-14.8
Reactive gastropathy	251 (38.3)	107 (34.9)	144 (41.3)	0.1	0.7	0.5-1.0
Non-infectious chronic gastritis	325 (49.6)	197 (64.3)	128 (36.7)	**<0.001**	3.1	2.2-4.2
Intestinal metaplasia	217 (33.1)	118 (38.5)	99 (28.4)	**0.007**	1.5	1.1-2.1
Glandular atrophy	175 (26.7)	103 (33.66)	72 (20.6)	**0.0002**	1.9	1.3-2.7
Helicobacter pylori gastritis	189 (28.8)	99 (32.3)	90 (25.8)	0.07	1.3	0.9-1.9
Duodenitis	29 (4.43)	11 (3.59)	18 (5.1)	0.3	0.6	0.3-1.4

Abbreviations: CI, confidence interval; NSAIDs, Nonsteroidal anti-inflammatory drugs; OR, odds ratio, PPIs, proton pump inhibitors;

veloping anemia by 2.2 times. Regarding gastrotoxic medication, antivitamin K oral anticoagulants were found to be independently associated with anemia (p=0.01). Among the comorbidities included in the logistic regression analysis, chronic kidney disease remained an independent predictor, increasing the odds of developing anemia by 4.9 times (Model 1).

In the multivariate logistic regression analysis, out of all the studied symptoms, none was found to be predictive of anemia. Epigastric pain (p<0.001, OR 0.4), heartburn (p<0.00, OR 0.1) and nausea/vomiting (p=0.01, OR 0.5) were statistically significantly more frequent in the non-anemic group (Model 2).

Since chronic kidney disease was more prevalent in anemic patients and represented an important confounder for anemia development, we analyzed the independent predictor role of mucosal defects, pathological findings, drugs, and comorbidities in patients with anemia and negative history for CKD. After excluding patients with CKD, the other parameters e.g. gastric erosions (p<0.001), gastric ulcer (p<0.001), non-infectious chronic gastritis (p<0.001), and antiplatelet administration (p<0.001) still predicted anemia (Model 3).

To identify other confounding variables impacting the earlier results, we further categorized patients according to simultaneous positive status for anemia and premalignant gastric lesions.

Anemic patients with premalignant gastric lesions were older than the patients without anemia and negative histology for premalignant gastric lesions (p<0.001). Also, they presented more often with cardiovascular diseases (p<0.001), chronic respiratory disease (p=0.0002), and chronic kidney disease (p<0.001), but no association was found with cerebrovascular, liver, and osteoarticular diseases (Table 2).

Antiplatelet drugs (p=0.01), antivitamin K anticoagulants (p<0.001), ACE inhibitors (p=0.006) and beta-blockers (p=0.0004) were statistically significantly associated with anemia and premalignant gastric lesions. Loss of appetite (p=0.01) and weight loss (p<0.001) were sta-

Model 1. Multivariate logistic regression model questioning the independent predictor role of mucosal defects, pathological findings, drugs and comorbidities in anemic patients

Variable	OR	95% IC	p value
Gastric erosions	2.5	1.6-3.9	**<0.001**
Gastric ulcer	8.1	4.6-14.3	**<0.001**
Non-infectious chronic gastritis	2.2	1.5-3.1	**<0.001**
Premalignant gastric lesions	1.1	0.7-1.6	0.5
Antiplatelets	1.1	0.7-1.7	0.4
Antivitamin K oral anticoagulants	2.3	1.2-4.6	**0.01**
Non-antivitamin K oral anticoagulants	1.5	0.7-3.1	0.2
NSAIDs	0.8	0.5-1.4	0.5
Chronic kidney disease	4.9	2.7-8.8	**<0.001**
Osteoarticular diseases	0.7	0.4-1.3	0.3
Chronic liver diseases	0.8	0.5-1.3	0.4

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 2. Multivariate logistic regression analyzing the predictive value of symptoms in anemic patients

Variable	OR	95% IC	p value
Epigastric pain	0.4	0.2-0.5	**<0.001**
Heartburn	0.1	0.1-0.3	**<0.001**
Bloating	0.8	0.5-1.3	0.4
Nausea/Vomiting	0.5	0.3-0.8	**0.01**
Loss of appetite	1.2	0.6-2.1	0.5
Weight loss	1.5	0.8-2.6	0.1

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 3. Multivariate logistic regression questioning the independent predictor role of mucosal defects, pathological findings, drugs and comorbidities in anemic patients without chronic kidney disease

Variable	OR	95% CI	p value
Gastric erosions	2.4	1.4-3.7	**<0.001**
Gastric ulcer	12.8	6.6-24.5	**<0.001**
Non-infectious chronic gastritis	1.9	1.3-2.8	**<0.001**
Premalignant gastric lesions	1.3	0.8-2.1	0.1
Antiplatelets	1.5	0.9-2.4	0.05
Antivitamin K oral anticoagulants	2.4	1.1-5.2	**0.02**
Non-antivitamin K oral anticoagulants	0.4	0.2-1.1	0.1
NSAIDs	0.99	0.01-2.5	0.9
Osteoarticular diseases	0.6	0.3-1.1	0.1
Chronic liver diseases	**0.9**	**0.5-1.6**	**0.9**

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

Table 2. Group differences regarding demographic, clinical, endoscopic and histological features in patients with anemia and premalignant gastric lesions versus non-anemic patients and negative histology for premalignant gastric lesions

Parameter	Total N=364 n(%)	Patients with anemia and premalignant gastric lesions N=129 n (%)	Non-anemic patients with negative histology for premalignant gastric lesions N=235 n (%)	p-value	OR	95% CI
Age > 65 years	168 (46.1)	92(71.3)	76 (32.3)	**<0.001**	5.2	3.2-8.1
Comorbidities						
Cardiovascular diseases	185(50.8)	91 (70.5)	94 (40)	**<0.001**	3.5	2.2-5.7
Cerebrovascular diseases	21(5.7)	10 (7.7)	11 (4.6)	0.2	1.7	0.7-3.9
Chronic respiratory diseases	50 (13.7)	30 (23.2)	20 (8.5)	**0.0002**	3.2	1.7-6.1
Diabetes mellitus	55 (15.1)	26 (20.1)	29 (12.3)	0.06	1.7	0.9-3.1
Arterial hypertension	283 (77.7)	84 (65.1)	119 (50.6)	0.008	1.8	1.1-2.8
Liver diseases	70 (19.2)	21 (16.2)	49 (20.8)	0.3	0.7	0.4-1.2
Osteoarticular disorders	57(15.6)	20 (15.5)	37 (15.7)	0.9	0.9	0.5-1.7
Chronic kidney disease	46 (12.6)	33 (25.5)	13 (5.5)	**<0.001**	5.8	3.0-11.9
Drug consumption						
Antiplatelet drugs	109(29.9)	49 (37.9)	60 (25.5)	**0.01**	1.7	1.1-2.8
Antivitamin K anticoagulants	40 (10.9)	27 (20.9)	13 (5.5)	**<0.001**	4.5	2.2-9.1
Non-antivitamin K oral anticoagulants	22(6)	12 (9.3)	10 (4.2)	0.06	2.3	0.9-5.4
ACE inhibitors	116 (31.8)	53 (41)	63 (26.8)	**0.006**	1.9	1.2-3.0
Beta-blockers	98 (26.9)	76 (58.9)	92 (39.1)	**0.0004**	2.2	1.4-3.4
NSAIDs	67 (18.4)	18 (13.9)	49 (20.8)	0.1	0.6	0.3-1.1
PPIs	218 (59.8)	87 (67.4)	131 (55.7)	**0.03**	1.6	1.0-2.5
Symptoms						
Epigastric pain	180 (4.9)	39 (30.2)	141(60)	**<0.001**	0.2	0.1-0.4
Heartburn	42 (11.5)	8 (6.2)	80 (34)	**<0.001**	0.1	0.06-0.2
Regurgitation	14 (3.8)	4 (3.1)	10 (4.2)	0.05	3.6	1.1-12.0
Nausea/Vomiting	69 (18.9)	19 (14.7)	50 (21.2)	0.1	0.6	0.3-1.1
Bloating	62 (17)	14 (10.8)	48 (20.4)	**0.02**	0.4	0.2-0.8
Early satiety	2 (0.5)	1 (0.7)	1 (0.4)	0.7	1.8	0.09-34.8
Loss of appetite	44(12)	23(17.8)	21 (8.9)	**0.01**	2.2	1.1-4.2
Diarrhea	21 (5.7)	5 (3.8)	16 (6.8)	0.3	0.5	0.2-1.5
Weight loss	42 (11.5)	27 (20.9)	15 (6.3)	<0.001	3.8	1.9-7.4
Endoscopic and histologic findings						
Erosions	83 (22.8)	51 (39.5)	32 (13.6)	**<0.001**	4.1	2.5-6.8
Ulcer	55 (15.1)	43 (33.3)	12 (5.1)	**<0.001**	9.2	4.6-17.6
Reactive gastropathy	148(40.6)	32 (24.8)	116 (49.3)	**<0.001**	0.3	0.2-0.5
Non-infectious chronic gastritis	158 (43.4)	87 (67.4)	71 (30.2)	**<0.001**	4.7	3.0-7.5
Helicobacter pylori gastritis	95 (26)	38 (29.4)	57 (24.2)	0.3	1.3	0.8-2.1
Duodenitis	18 (4.9)	5 (3.87)	13 (5.5)	0.6	0.6	0.2-1.8

Abbreviations: CI, confidence interval; NSAIDs,nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; OR, odds ratio.

tistically significant more frequent in patients with anemia and premalignant gastric lesions, while epigastric pain (p<0.001), heartburn (p<0.001), and bloating (p=0.02) were more frequent in non-anemic patients and negative histology for premalignant lesions.

The patients with anemia and premalignant gastric lesions presented more often gastric erosions, gastric ulcer along with non-infectious chronic gastritis (p<0.001). Reactive gastropathy was more frequent in the non-anemic participants (p<0.001). No association was found between anemic patients with premalignant gastric lesions and *H. pylori* infection or duodenitis (all p>0.05) (Table 2).

In patients over 65 years, chronic kidney disease continued to be an independent predictor for anemia and the concomitant presence of premalignant gastric lesions in the multivariate logistic regression analysis. Regarding gastrotoxic medication, anti-vitamin K oral anticoagulants were found to be independently associated with anemia and the presence of premalignant gastric lesions (p=0.03). Weight loss was found to be predictive of anemia in the presence of premalignant gastric lesions (p=0.006). Epigastric pain (p<0.001) and heartburn (p<0.001) were statistically significantly more frequent in the non-anemic group (Model 4).

In model 5 of multivariate logistic regression, gastric erosions (p<0.001), gastric ulcer (p<0.001) and non-infectious chronic gastritis (p<0.001) remained statistically significant in the multivariate logistic analysis. Also, antivitamin K anticoagulants were statistically significantly more frequent in anemic patients with premalignant gastric lesions (Model 5).

In the last regression model, we analyzed the predictor role of mucosal defects, pathological findings, drugs and comorbidities in patients with anemia and premalignant gastric lesions, excluding patients with CKD. After excluding these patients, the other parameters e.g. gastric

erosions (p<0.001), gastric ulcer(p<0.001), non-infectious chronic gastritis (p<0.001), and anti-vitamin K oral anticoagulants(p=0.04) remained independent predictors (Model 6).

Discussions

The research investigated clinical, histological, and endoscopic features in relation to anemia, irrespective of its type, in patients endoscopically evaluated for digestive complaints, including unintentional weight loss and decreased/loss of appetite, in the absence of active bleeding signs or a lower digestive tract disease, in order to improve surveillance and management strategies.

Non-infectious chronic gastritis was found to be an independent predictor for anemia and premalignant gastric lesions. Conditions that can lead to non-infectious chronic gastritis are autoimmune gastritis (usually associated with anti-parietal cell antibodies), various chemicals (chronic bile reflux, administration of NSAIDs and aspirin, cocaine, etc.), and chronic or acute renal failure [11]. Vitamin B12 and/or iron deficiency anemia may occur in both chronic atrophic gastritis due to *H. pylori* infection or autoimmune gastritis due to achlorhydria and malabsorption [13]. Chronic blood loss may determine IDA, which is usually asymptomatic for long periods of time [14].

We stratified patients according to concomitant positive status for premalignant lesions and anemia in order to clarify possible confounding factors influencing the previous results. Among concomitant histological lesions, only chronic gastritis reached the threshold of statistical significance in these patients. In the absence of inflammatory changes, reactive gastropathy seems to be negatively associated with anemia and premalignant gastric lesions.

Endoscopic lesions (gastric erosions and ulcer) remained independent predictors for concomitant anemia and premalignant lesions in a model adjusted for gastrotoxic drugs and histologic lesions.

Epigastric pain and heartburn were negatively correlated with anemia, whether is associated or not with premalignant lesions, confirming that patients with precancerous lesions are not experiencing symptoms. Some studies suggest that anemic patients presented more often dyspepsia [15] along with other GI complaints [16]. Almost a third of patients with chronic atrophic gastritis, gastric polyps, or ulcers were asymptomatic, leading to a delay in diagnosis and treatment in other studies [17]. Dyspepsia can't be

Model 4. Results from multivariate logistic regression analyzing the predictive value of age, comorbidities, medication and symptoms in patients with concomitant anemia and premalignant gastric lesions

Variable	OR	95% IC	p value
Age > 65 years	6.8	3.7-12.6	**<0.001**
Cardiovascular diseases	1.1	0.5-2.0	0.7
Chronic respiratory diseases	1.9	0.9-4.0	0.05
Chronic kidney disease	2.7	1.2-5.7	**0.01**
Anti-vitamin K oral anticoagulants	2.3	1.0-5.3	**0.03**
Antiplatelets	1.0	0.5-1.8	0.9
Proton pump inhibitors	1.4	0.8-2.4	0.1
Epigastric pain	0.3	0.2-0.5	**<0.001**
Heartburn	0.1	0.07-0.3	**<0.001**
Bloating	0.9	0.4-1.9	0.8
Inappetence	1.1	0.5-2.5	0.7
Weight loss	3.1	1.3-7.3	**0.006**

Abbreviations: CI, confidence interval; OR, odds ratio.

Model 5. Results from multivariate logistic regression analysis regarding endoscopic and histologic lesions along with medication in patients with anemia and concomitant premalignant gastric lesions

Variable	OR	95% IC	p value
Gastric erosions	3.0	1.5-5.7	**<0.001**
Gastric ulcer	7.4	3.3-16.2	**<0.001**
Reactive gastropathy	0.5	0.2-1.0	0.05
Helicobacter pylori gastritis	1.1	0.4-2.4	0.2
Non-infectious chronic gastritis	7.8	3.7-16.2	**<0.001**
Anti-vitamin K oral anticoagulants	2.8	1.1-6.7	**0.02**
Antiplatelets	1.6	0.9-2.9	0.08

Abbreviations: CI, confidence interval; OR, odds ratio

Model 6. Multivariate logistic regression questioning the independent predictor role of mucosal defects, pathological findings, drugs and comorbidities in anemic patients with premalignant gastric lesions and a negative history of CKD

Variable	OR	95% IC	p value
Gastric erosions	3.9	1.9-7.7	**<0.001**
Gastric ulcer	9.6	4.0-23.3	**<0.001**
Reactive gastropathy	0.6	0.2-1.3	0.2
Helicobacter pylori infection	1.2	0.6-2.7	0.3
Non-infectious chronic gastritis	7.0	3.0-16.3	**<0.001**
Anti-vitamin K oral anticoagulants	1.9	1.0-3.7	**0.04**
Antiplateles	2.0	0.7-5.5	0.1

Abbreviations: CI, confidence interval; OR, odds ratio"

linked to *H. pylori* infection, as *H. pylori*-positive individuals with dyspeptic symptoms shared the same clinical characteristics as the uninfected group [18]. Functional dyspepsia may be aggravated by various psychosocial factors and psychiatric conditions [19], somatization, or depression [20]. Our study confirmed the decreased risk of anemia and significant clinical and histologic gastro-duodenal changes in patients with dyspeptic symptoms. Weight loss was also associated with anemia in our study, along with decreased appetite. In multivariate analysis of a study that included 91 patients with IDA, advanced age, male gender, and weight loss were associated with GI lesions in all patients [21] In our study, weight loss remained an independent predictor for simultaneous anemia and premalignant lesions, underlying the importance of endoscopy even if neoplasia is ruled out [22].

Anemia is frequent in elderly patients, especially in the presence of premalignant gastric lesions. *H. pylori* infection has a higher incidence in older people and is the main risk factor for gastric cancer [23], causing lesions of the mucosa, atrophy, and impaired microcirculation [24]. Mitochondrial dysfunction and disrupted nuclear-mitochondrial communication [25], hypoxia [26], apoptosis [27], and high levels of reactive oxygen species are responsible for the abnormal functionality of an aging stomach. In our research, anemic patients presented more often with cardiovascular diseases, including arterial hypertension, chronic respiratory disease, diabetes mellitus, and chronic kidney disease. In the presence of premalignant gastric lesions, these comorbidities continued to be linked to anemia. The multivariate regression analysis showed that cardiovascular disease and respiratory disease lost statistical significance in patients that were 65 years of age or older, implying that age > 65 years was a confounding factor. Diabetes mellitus is no longer significantly correlated with anemia in the presence of premalignant gastric lesions, with other studies demonstrating different results [28], [29].

Therapy with antivitamin K anticoagulants is an independent predictor for anemia alone or associated with premalignant lesions, while antiplatelet medication or non-antivitamin K therapy lost statistical significance in the presence of chronic disease (cardiovascular, respiratory, or renal). The results highlight the importance of the use of direct anticoagulants with an improved safety profile whenever is possible. The difficult control of the therapeutic effect of anti vitamin K may promote small bleeding episode from different site of digestive tract generating anemia in vulnerable patients. Dicoumarol may determine also eryptosis by encouraging Ca(2+) entrance, which leads to the Ca(2+)-dependent cell membrane scrambling [30]. In patients treated with anticoagulants for atrial fibrillation, warfarin administration led to higher rates of bleeding events compared with apixaban in patients with or without anemia. New-onset anemia had a significantly higher incidence in patients randomized to warfarin compared with those randomized to apixaban [31]. High rates of major hemorrhage on warfarin were reported, especially in elderly patients [32].

PPI consumption was present more frequently in the study group, maybe for symptom control and co-administration with gastro-toxic medication, but it is not a predictor for anemia, associated or not with premalignant lesions. In our study group, 10.78% of patients are taking antivitamin K anticoagulants concomitant with PPI (compared to 2.01% in the control group), 6.54% of patients are treated with NOACs along with PPI (compared to 2.87 in the control group), and 11.11% of patients are taking NSAIDs simultaneously with PPI (compared to 0% in the control group).

By increasing the odds of developing anemia by 4.9 times, chronic kidney disease represents an important predictor for anemia and a possible confounding factor. After excluding patients with CKD, gastric lesions (e.g. erosions, ulcer, and non-infectious chronic gastritis) continued to be independent predictors of anemia, even in the presence of premalignant gastric lesions.

Our study emphasized that patients with chronic inactive gastritis and premalignant gastric lesions, probably after unintentional clearance of *H. pylori* infection and/or after exposing to chemical mucosal aggressors are more prone to develop anemia, while reactive gastropathy and dyspeptic symptoms seem to be negative predictors. The limitations of the study are: studied groups are too small to adequately represent variations among all investigated parameters and all participants were investigated in the same center, their sociodemographic features being similar; serum ferritin, transferrin, B12, and folate levels were not studied as not all parameters were available in selected patients; we haven't excluded liver diseases that could impact the absorption of micronutrients (for example, alcoholic liver disease promotes vitamin B12, vitamin B6, and folate deficiency [33]. Nonetheless, the study demonstrated the high frequency of anemia in patients referred for EGD without bleeding signs or symptoms in the absence of lower digestive tract diseases. Assessing the usual clinical and pathological parameters and clarifying relevant predictors for anemia, our results may contribute to improvement of surveillance and preventive strategies as well as to interdisciplinary approach of patients with GI symptoms.

Conclusions

In patients without bleeding signs evaluated on endoscopy for digestive symptoms, chronic inactive gastritis, and premalignant gastric histologic lesions are associated with anemia, while active *H. pylori* infection is not. Antivitamin K therapy, but not antiplatelet, non-antivitamin K anticoagulants or NSAIDs are independent predictors for anemia in an endoscopic population without bleeding signs. Epigastric pain and heartburn are inversely associated with anemia alone or associated with premalignant gastric lesion in patients investigated on endoscopy. Chronic inactive gastritis predicts concomitant anemia and premalig-

nant lesions, while reactive gastropathy has a borderline negative association with the simultaneous presence of these conditions.

Authors' contributions

SNM (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing)
AC (Conceptualization; Formal analysis; Investigation; Project administration; Supervision; Writing – original draft; Writing – review & editing)
SM (Data curation; Investigation; Project administration; Resources; Validation)
RR (Data curation; Investigation; Methodology; Writing – original draft;)
ZT (Data curation; Investigation; Methodology; Writing – original draft;)
RP (Data curation; Investigation; Methodology; Writing – original draft;)
AN (Conceptualization; Formal analysis; Investigation; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

Conflict of interest

The authors state that they have no conflict of interest.

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