Doctoral school in Medical Sciences

As a manuscript
C.Z.U: 616.33-002.27-07(043.2)

BOTEZATU Adriana

CLINICAL, SEROLOGICAL AND MORPHOLOGICAL MANIFESTATIONS AT PATIENTS WITH CHRONIC ATROPHIC GASTRITIS

321.01 - INTERNAL DISEASES (GASTROENTEROLOGY, HEPATOLOGY)

Summary of the doctoral thesis in medical sciences

Chisinau, 2021

The thesis was elaborated at the Department of Internal Medicine (Discipline of Geriatrics and Occupational Medicine) of the *"Nicolae Testemitanu"* Public Institution State University of Medicine and Pharmacy and in the Department of Internal Diseases of the Public Medical Institution Clinical Hospital of the Ministry of Health, Labour and Social Protection.

Scientific adviser

BODRUG Nicolae,
habilitated doctor of medical sciences,
university professor _____ *signature*

Official references:

SCORPAN Anatolie, doctor of medical sciences, associate professor
DUMITRAȘCU Dan L., doctor of medical sciences, university professor (Cluj-Napoca, Romania)
UNGUREANU Bogdan, doctor of medical sciences, associate professor (Craiova, Romania)

Componence of the Commission for public defense of the doctoral thesis:

Curocichin Ghenadie, chairman, habilitated doctor of medical sciences, associate professor
Peltec Angela, secretary, doctor of medical sciences, associate professor
Bodrug Nicolae, member, habilitated doctor of medical sciences, university professor
Tcaciuc Eugen, member, habilitated doctor of medical sciences, associate professor
Gheonea Dan, member, doctor of medical sciences, university professor (Craiova, Romania)

The presentation will take place on 13.05.2021, at 14:00, in the meeting of the Specialized Scientific Council D 321.01-21-3 within the State University of Medicine and Pharmacy "Nicolae Testemitanu" (bd. Ştefan cel Mare şi Sfânt, 165, Chisinau , MD-2004, Republic of Moldova). The doctoral thesis in medical sciences and the abstract of the paper can be consulted at the library of the State University of Medicine and Pharmacy "Nicolae Testemitanu", 29 Testemitanu Street and on the ANACEC website (www.cnaa.md).

The abstract was sent on April 12, 2021.

Scientific Secretary of the Specialized Scientific Council:
doctor of medical sciences, Associate professor _____ **PELTEC Angela**
Scientific adviser:
Habilitated doctor of medical sciences,
university professor _____ **BODRUG Nicolae**

Author _____**BOTEZATU Adriana**

CONTENT

INTRODUCTION

Actuality and importance of the research: Although the incidence of gastric cancer (GC) has decreased significantly in the last century, partly due to effective eradication and reduced prevalence of *H. pylori* (HP), the disease is still one of the leading causes of cancer death worldwide [13, 24, 44]. In the latest global cancer statistics, the disease ranks 5th after incidence (8% of the total number of cancers) and is the 2nd leading cause of cancer death in both sexes (10% of total deaths caused by neoplasms) [32, 43]. In Romania, gastric cancer is the 6th malignant localization in both sexes, with an incidence of 5.2% [32]. Only 1-3% of people infected with HP develop GC [44].

Upper digestive endoscopy (UDE) with biopsy is the "gold standard" for the diagnosis of GC and precancerous gastric lesions (chronic atrophic gastritis (CAG), intestinal metaplasia (IM), gastric epithelial dysplasia (GED)), but their use population-based screening is limited due to the invasiveness of the method and the cost, but for high-risk patients it remains the only strategy available [10, 21, 26, 38]. While many aspects of gastritis pathology remain to be elucidated, consistent information indicates that CAG is the only, strongest predictor of the onset of intestinal IM and GC [10]. Early diagnosis of gastric precancerous lesions in the general population and surveillance of these patients are important considerations for early identification and reduction of GC mortality, increased survival rate and improved quality of life of patients [8, 9, 13]. However, at this moment, premalignant changes in the gastric mucosa are often ignored in clinical practice or result in a variable frequency of surveillance or treatment [31].

Thus, based on the above, the purpose of this study is to elucidate the clinical/para-clinical manifestations in patients with chronic atrophic gastritis depending on the morphological type of existing gastric lesion.

In order to achieve the goal, the following general research objectives were stipulated:

1. Evaluation of clinical features in patients with chronic atrophic gastritis.
2. Determination the correlation between the severity of gastric mucosal damage in chronic endoscopic atrophic gastritis and the stage of gastric mucosal atrophy according to the OLGA and OLGIM systems.
3. Estimation of the role and value of non-invasive serological diagnosis in the prognosis of chronic atrophic gastritis.
4. Study of the relationship between morphological examination and functional activity of the gastric mucosa by determining the concentration of serological markers, followed by comparison of morphological and serological data.
5. Elaboration of a diagnostic algorithm for patients with chronic atrophic gastritis.

The general research methodology was developed based on the publications of local authors [10, 17, 19] and abroad [7, 28]. In this cross-sectional cohort clinical trial, patients were selected according to inclusion and exclusion criteria. For the research and solution of the problems approached in the thesis we used the methods: analytical epidemiological, investigation, clinical examination, para-clinical investigations, statistical, mathematical procedures, monitoring and evaluation tools.

Scientific novelty of the obtained results: The clinical, serological and morphological features of CAG were highlighted depending on the degree of damage to the gastric mucosa. The

correlation between invasive and non-invasive tests in the diagnosis of CAG was evaluated, with the estimation of the role of HP, the severity of the clinical picture and the foveolar pattern of the gastric mucosa. Physiological, morphological and clinical research has deepened data on the characteristics of gastric precancerous conditions in relation to the inflammatory activity of the gastric mucosa, streamlined the diagnosis of the disease and increased the specificity of screening for patients at high risk of developing gastric precancerous pathology.

The applicative value of the study consists in the elaboration of an algorithm for early diagnosis of CAG in order to prevent gastric cancer. Recommendations have been proposed for the examination of patients infected with HP (immunological testing and histological staging of CAG) to isolate cohorts with a high risk of developing GC.

Approval of the thesis results. The results of the study were presented and discussed in the following national and international scientific forums:

1. Annual Conference of the University of Medicine and Pharmacy of Iasi "Gr T. Popa" "Contemporary aspects in chronic atrophic gastritis", March 4-06, 2016, Iasi, Romania.
2. The third Congress of Internal Medicine "News in gastric precancerous lesions", October 24-25, 2017, Chisinau, Republic of Moldova.
3. Centenary Symposium of Romanian Internal Medicine in Cluj "Premalignant lesions and gastric cancer", October 24-26, 2019, Cluj-Napoca, Romania.
4. Meeting of the Romanian Society of Neurogastroenterology "Identifying precancerous lesions - an important step in gastric cancer prevention", 07-09 November 2019, Iași, Romania.
5. University Days and Annual Scientific Conferences of collaborators and students of USMF IP "Nicolae Testemiţanu", 2014, 2017, 2018, 2019, Chisinau, Republic of Moldova.
6. III Russian Gastroenterology Congress with international participation "Gastroenterology of Russia from birth to old age (pediatric, therapeutic, surgical and medico-social aspects)", "Precancerous diseases and stomach cancer". 29-30 October 2020, Saint-Petersburg, Russia.

The positive opinion of the Research Ethics Committee for the study was received on June 17, 2019 (the act nr. 38).

Keywords: chronic atrophic gastritis, atrophy of the gastric mucosa, intestinal metaplasia, gastric epithelial dysplasia, advanced upper digestive endoscopy, morphological examination, Helicobacter pylori.

Thesis publications. The materials of the thesis were reflected in 13 scientific papers, including 3 articles without co-authors and 8 articles in reviewed editions, 11 active participations with communications and posters at international and national scientific forums, a patent.

The volume and structure of the thesis. The paper is presented on 155 pages of text, consists of introduction, 4 chapters, general conclusions, practical recommendations and bibliographic index with 237 references. The illustrative material includes 39 figures, 25 tables, 4 statistical formulas and 6 annexes.

1. CONTEMPORARY ASPECTS REGARDING DIAGNOSIS AND PROGNOSIS OF CHRONIC ATROPHIC GASTRITIS

1.1. Definition, classification and epidemiology of chronic atrophic gastritis

Definition. CAG is a chronic inflammatory condition, characterized by loss of gastric glandular structures [13, 20, 24, 30, 44]. Current perception of gastric mucosal atrophy (GMA) includes two different phenotypes: (1) obvious disappearance of glandular units associated with fibrotic expansions in the *lamina propria* - reduced glandular mass without changes in the original epithelium (CAG by apoptosis) and (2) metaplastic replacement of native glands with glands contained ectopic cell arrangement (intestinal metaplasia and/or pseudo-pyloric metaplasia - CAG by substitution) [9, 10, 14, 36].

Classification. In accordance with the Sydney system, CAG is classified according to severity: (1) CAG is missing, (2) mild CAG (gastric antral atrophy), (3) moderate CAG (extension to less curvature from the middle of the gastric body) and (4) Severe CAG (pangastritis) [13, 32]. Although the updated Houston version of the Sydney classification is the most widely used classification of gastritis, it does not express the gradation of GC risk in patients with CAG [31]. In the Kimura-Takemoto classification there are three degrees of endoscopic CAG: missing (C0), mild (C1-C2), moderate (C3-O1) and severe (O2-O3) [34, 35]. In type C1 atrophic changes are not visible in the corpus and are visible only in the antrum. In types C2 and C3 the border of atrophy is on the less curvature in the lower and upper part of the gastric body, respectively. In type O1 the atrophic border is between the less curvature and the anterior wall of the gastric body. In O2 atrophic changes extend on the anterior wall, and in O3 the limit is between the anterior wall and the large curvature [25, 34].

Epidemiology. Epidemiological data on the incidence and prevalence of HP, CAG, IM and GED infection in different parts of the world are scarce, especially from population-based studies. These lesions are difficult to assess due to the fact that they often remain clinically asymptomatic, can only be detected in UDEs by histological examination of biopsies and, in part, difficult due to inadequate biopsy sampling [1, 2, 9, 31]. However, the epidemiology of premalignant gastric lesions is important due to their relationship with GC and the need to improve screening and surveillance strategies [18].

Prevalence of Helicobacter pylori infection. HP infection is diagnosed on average in 50% (5-80% in the general population worldwide) [15, 32, 40, 42]. The HP toll remains debatable in the literature [13, 15, 23, 32, 42].

The prevalence of chronic atrophic gastritis worldwide correlates with age, is higher in men, has considerable geographical and ethnic differences, and is frequently associated with HP, especially with virulent CagA strains [23, 29]. The first line of diagnosis of CAG is UDE or diagnosis based on serum PG. Confirmation is made in advanced endoscopy with methodical and optically-guided biopsy. However, in general, CAG remains underdiagnosed [9, 31, 43]. Studies conducted in areas with a high incidence of CAG (Japan, China) showed a prevalence between 33% and 84% [9, 43].

1.2. Pathophysiology and symptomatology of chronic atrophic gastritis

Pathophysiology. The development of intestinal gastric adenocarcinoma is the final stage of the succession of inflammation - atrophy - metaplasia - dysplasia - carcinoma, named Correa cascade

for gastric carcinogenesis. This model is confirmed by a considerable number of longitudinal clinical-pathological and epidemiological studies [41].

Symptomatology of chronic atrophic gastritis. The clinical spectrum of CAG is not clearly defined and is often nonspecific, with an overlap of the clinical features of the two entities of CAG - autoimmune and associated with HP infection. Thus, in contrast to the classic perception of a silent condition, patients with CAG report a wide range of gastrointestinal symptoms, ranging from dyspeptic symptoms to symptoms of gastroesophageal reflux [20, 23].

Risk factors for CAG, IM and GC are: HP infection, genetic factors (age, duration of HP infection, male sex, hereditary collateral history of GC), ulcer disease, enterogastric reflux, smoking, alcohol dependence, use prolongation of proton pump inhibitors and non-steroidal anti-inflammatory drugs, diet (diet low in fruits, vegetables and vitamin C, excessive salt consumption and consumption of salt preservatives) [12, 37, 40, 43].

1.3. Contemporary methods for early diagnosis of chronic atrophic gastritis

At this stage there are three main methodological approaches for the early diagnosis of CAG: 1. Serological examination - markers of gastric function: PG-I, PG-II, PGR, G-17 and HP-IgG determination. 2. Advanced endoscopic examination with special techniques (high resolution, special spectrum illumination, endoscopic magnification, endoscopy and optically guided biopsy). 3. Histological and histochemical examination to confirm serological and endoscopic data [21, 26, 38].

2. STUDY MATERIAL AND METHODS

2.1. General feature of the research methodology

To estimate the particularities of early diagnosis and prognosis of CAG in order to prevent GC, a cross-sectional cohort clinical study was performed, based on: (1) evaluation of clinical, serological and morphological features in patients with CAG, compared to (2) visible gastric mucosal changes in the method of advanced digestive endoscopy. Patient data were coded in specially developed sheets for statistical processing.

The volume of the representative sample was calculated in the EpiInfo 7.2.2.6 Program, "StatCalc - Sample Size and Power" section for the analytical study based on the following parameters:

1. The confidence interval for 95.0% significance of the results.

2. Statistical power - 80.0%.

3. The global prevalence of CAG in the general population is on average 33.0% (26-41%) in endoscopic studies with biopsies [27].

For the 95.0% confidence interval, the calculated value of the sample is 25 patients, after adjusting the design effect (sex, age, clinical form, serological outcome, risk factors) - 125 patients and including the rate of non -response of 10.0% - 138 patients.

Thus, the sample was representative for an error allowed of 5% and included 142 patients, more than the representative minimum limit value of 138 patients. The research was carried out in several stages, respecting the inclusion and exclusion criteria:

Step 1. Patients included in the study were investigated para-clinically (laboratory methods and exploration instruments) and clinically. Following the results obtained, the self-division was performed according to the clinical form of the disease.

Step 2. Statistical processing of the obtained results.

Step 3. Evaluation of the basic indicators that characterize the study groups. Comparative estimation of endoscopic changes, clinical and serological features depending on the type morphology of the lesion with the development of an algorithm for early diagnosis of patients with CAG for cancer prevention.

Step 4. Presentation of results.

Criteria for inclusion in the study: patients with CAG, morphologically confirmed; patients aged 18 years and over; patients with a previous or current HP infection; patients diagnosed with CAG not more than 5 years; patients who read and signed the informed consent to the study.

Exclusion criteria from the study: patients under 18 years of age; patients with malignant tumors; patients with severe associated comorbidities that affect the course of the underlying disease (central nervous system pathology, organic diseases of the endocrine glands, severe heart failure, severe liver dysfunction, severe renal dysfunction, severe lung dysfunction, haematological disorders, conditions requiring medical administration); pregnant women, midwives and lactating women; patients with severe coagulation disorders: INR> 3; platelets <30,000/Mmc; patients with active digestive bleeding; patients with a history of gastric surgery. In the research were enrolled 142 patients with CAG selected consecutively in the Internal Diseases section of IMSP Clinical Hospital of the Ministry of Occupational Health and Social Protection. The general study group was divided into 3 subgroups depending on the morphological type of the lesion: subgroup 1 - 51 patients with CAG, without MI and without GED, subgroup 2 - 51 patients with CAG and IM and subgroup 3 - 40 patients with CAG and GED.

2.2. General characteristic of study groups

Patients in all 3 study subgroups were age-appropriate. The mean age in subgroup 1 of study was 54.94 ± 1.9 years, in subgroup 2 of study - 57.39 ± 1.4 years and in subgroup 3 of study - 59.45 ± 1.7 years (p> 0.05). The distribution of patients in the study subgroups by age group was also wide in all 3 study groups (Table 1).

Table 1. **Distribution of patients with CAG from the study subgroups depending on age groups**

Age groups	**Study subgroup 1**		**Study subgroup 2**		**Study subgroup 3**		**p**
	abs.	**%**	**abs.**	**%**	**abs.**	**%**	
<45 years	10	19,6	4	7,8	4	10,0	>0,05
45-64 years	28	54,9	35	68,6	22	55,0	>0,05
≥65 years	13	25,5	12	23,5	14	35,0	>0,05

Socio-demographic data (living environment, educational level, martial status, socio-professional category) of patients from all study subgroups were statistically significant. In study subgroup 2, compared to study subgroup 1, statistically significant were more men (51.0% and 21.6%, respectively; p<0.01) and fewer women (49.0% and 78,4%, respectively; p <0.01) (Table 2).

Table 2. **General characteristic of patients with CAG from the study subgroups**

Parameter	Study subgroup 1 (1)		Study subgroup 2 (2)		Study subgroup 3 (3)		p
	abs.	%	abs.	%	abs.	%	
Gender:							
- mens	11	21,6	26	51,0	18	45,0	1-2**
- women	40	78,4	25	49,0	22	55,0	1-2**
Residential status:							
- urban environment	32	62,7	34	66,7	24	60,0	
- rural environment	19	37,3	17	33,3	16	40,0	
Studies:							
- primary	9	17,6	6	11,8	6	15,0	
- medium	21	41,2	29	56,9	18	45,0	
- superior	21	41,2	16	31,4	16	40,0	
Marital status:							
- married	38	74,5	40	78,4	23	57,5	
- unmarried	5	9,8	3	5,9	3	7,5	
- Widower	3	5,9	3	5,9	10	25	
- divorced	5	9,8	5	9,8	4	10,0	
Social group:							
- employee	34	66,7	34	66,7	22	55,0	
- Unemployed	3	5,9	-	-	2	5,0	
- not valid	3	5,9	1	2,0	1	2,5	
- retired	11	21,6	16	31,4	15	37,5	

Note: *statistically significant differences ** - p<0,01*

2.3. Investigation methods and diagnostic criteria.

Clinical methods. The accumulation of primary data was performed by applying the elaborated structured questionnaire, extracting data from medical documentation, the results of the primary visit and repeated visits, clinical and para-clinical investigations.

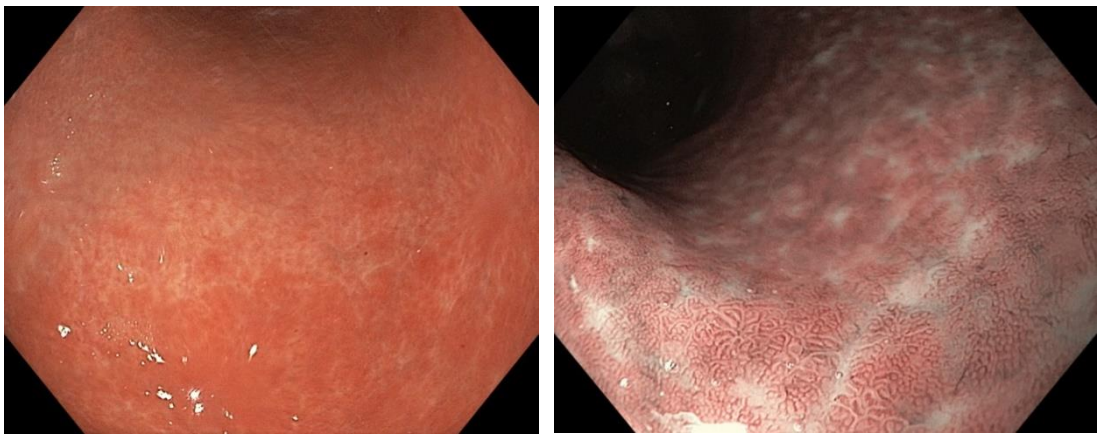
Biochemical methods. Blood was collected from the patients' ulnar veins in the first half of the day after 12 hours of fasting. Blood samples were immediately centrifuged at 4 ° C, obtaining 5 ml of stored serum (within 2 hours of collection) at -70 ° C until testing (within 6 months).

GastroPanel biomarkers - pepsinogen-I (PG-I), pepsinogen-II (PG-II), gastrin-17 (G-17) and antibodies to Helicobacter pylori IgG (HP-IgG) - were determined with commercial GastroPanel® enzyme immunoassays (Analyzer: Seac-Radim, Alisei QS, Italy) in accordance with the manufacturer's instructions, and the pepsinogen-I / II (PGR) ratio was calculated. Serum PGs were determined for the diagnosis of CAG. GMA was considered 'absent' (PG- I> 70 μg / l or PG- I / II> 3), 'mild' (PG- I ≤70 and> 50 μg / l and PG- I / II ≤3 and> 2), 'moderate' (PG- I≤50 and> 30 μg / l and PG- I / II≤3 and> 2) and 'severe' (PG- I≤30 μg / l and PG- I / 2) [8].

The current HP infection was found by two methods: 1) histological evidence of HP infection by Giemsa staining and 2) urease test. To distinguish the previous infection from the

current HP infection, we used two methods: 1) measuring the level of serum HP-IgG and 2) checking the history of treatment to eradicate the HP infection.

Instrumental methods. For the purpose of diagnosing CAG, the following investigations were performed: 1. Upper digestive endoscopy (UDE) and collection of gastric mucosa biopsies were performed on the Olympus® Evis Exera III endoscopic system with high performance endoscope (GIF-HQ190, Olympus Medical Systems Corp., Tokyo, Japan), with intravenous anesthetic support and spontaneous breathing. All patients were examined by a single endoscopist with special training. In all cases, meticulous examination of the gastric mucosa was performed under advanced HD-Near Focus-WLE-NBI^{+} imaging.



A B

Figure 1. *Endoscopic images representative of chronic atrophic gastritis A - in HD-Near Focus-WLE regime, the antral region has a thin and transparent mucosa with accentuation of the submucosal vasculature, foveolar pattern represented by small foveae, surrounded by fine capillary network, with orderly arrangement of subepithelial capillaries, honeycomb-like, which is interspersed with a network of spider-like microvenules composed of collecting venules. B - in HD-Near Focus-NBI + regime where the gastric mucosa is thin, transparent, alternating with large areas without foveolar structure and gastric glands with excessive highlighting of the submucosal vascular system, microvascular architecture characterized by rolling, wavy, altered vessels sectors of the ultrafine microvascular network.*

The tissue for biopsy was collected according to the OLGA / OLGIM protocol. The biopsies from each area were placed in separate marked containers [3, 4]. Gastric mucosal atrophy (GMA) was evaluated endoscopically according to the Kimura-Takemoto classification: atrophy is missing (C0), mild atrophy (C1-C2), moderate atrophy (C3-O1) and severe atrophy (O2-O3) [5, 6].

1. Morphological examination. The sampled tissues were fixed for 24-48 hours in 10% buffered neutral formalin and subsequently included in paraffin wax, the histological sections were cut to a thickness of 3 μm. Usual staining methods were used (hematoxylin and eosin according to Carazzi, picrofuxin according to the van Gieson method). Additional IM staining techniques were used to characterize IM: Alcian blue pH 2.5/Schiff acid periodic alkian, Alcian blue-colloidal iron/Alcian blue pH 2.5. Chronic inflammation and activity, HP, CAG, IM, GED or GC were determined in each biopsy specimen. The final diagnosis included the most severe histological lesion of all biopsies analyzed. HP infection was considered positive in the presence of bacteria in at least one of the five biopsies analyzed [2].

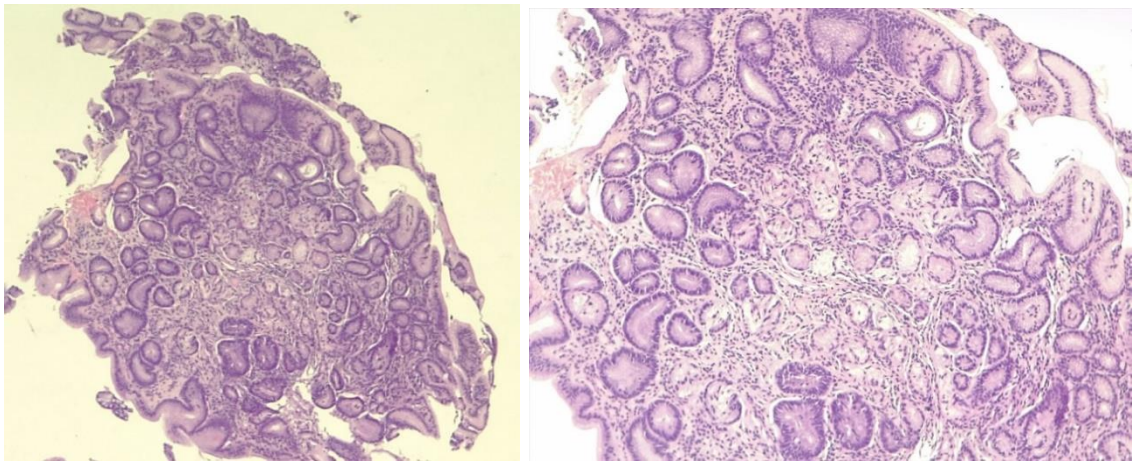


Figure 2. *Biopsy fragment of antral gastric mucosa, covered by columnar unistratified epithelium, with foveoles and pyloric glands, with moderate atrophy. Lymphocytic infiltrate is found in the connective tissue of the lamina propria.*

The histopathological examination was performed by two anatomo-pathologists, one of whom had more than 15 years of experience who did not know the identity of the samples and did not have access during the examination to the clinical, biological and endoscopic data of the subjects.

Methods of statistical processing of results. Primary data processing was performed using the functions and modules of SPSS version 16.0 for Windows (SPSS Inc., Belmont, CA, USA, 2008) and Microsoft Office Excel 2019 on the personal computer through descriptive and inferential statistical procedures. To estimate the significant differences between the means of two groups, the t test was used for independent samples, and between the group means - the t test for pair-samples. For multiple comparisons (3 or more) we used the analysis of variance (One-Way ANOVA) with the application of post-hoc tests or the non-parametric Kruskal-Wallis test with the application of Bonferroni correction. To assess the degree of intensity of statistical links we used the correlation procedure. Contingency table data were analyzed by the method of variational statistics (χ^2). Statistically significant we considered the differences with the bilateral value $p<0.05$.

3. CLINICAL-PARACLINICAL MANIFESTATIONS REGISTERED IN PATIENTS WITH CHRONIC ATROPHIC GASTRITIS ACCORDING TO THE MORPHOLOGICAL TYPE OF THE INJURY: Comparative analysis of clinical, serological and morphological features in the study subgroups

Subgroup 1 included CAG cases, without IM and without GED, subgroup 2 included CAG and IM cases, subgroup 3 included CAG and GED cases. Comparative analysis of socio-demographic characteristics in patients with different morphological type of CAG found that in study subgroup 1, compared to study subgroup 2, there were statistically significantly fewer men (21.6% and 51.0%, respectively; $p<0.01$) and statistically significant more women (78.4% and 49.0%, respectively; $p<0.01$).

All 3 study subgroups were classified according to age characteristics, environment and living conditions, marital status, education, social group, activity character, weight loss and family history of GC. There was a tendency to increase the mean value of age concomitantly with the

morphological worsening of CAG: 54.94 ± 1.9 years in patients in study subgroup 1, 57.39 ± 1.4 years in patients in study subgroup 2, and 59.45 ± 1.7 years in patients in study subgroup 3.

The evaluation of CAG risk factors revealed that in study subgroup 3, compared to study subgroup 2, there were statistically significant more people who frequently consumed (6-7 times a week) vegetables (22.5% and 2.0% , respectively; p<0.01) and frequently administered (6-7 times per week) non-steroidal anti-inflammatory drugs, including antiplatelet aspirin (60.0% and 27.5%, respectively; p<0.01), in study subgroup 1 there were statistically significant more non-smokers (70.6% and 45.1%, respectively; p<0.01), compared to study subgroup 2, and more normal-weight people (68.6% and 32.5%, respectively; p<0.01), compared to study subgroup 3. Although all patients in all 3 study subgroups reported present or supported HP infection, there was only a tendency to reduce the frequency of current HP infection and a tendency to increase the frequency of HP infection with a history of CAG worsening.

The frequency of previous treatment for HP infection was even higher in patients in all 3 study subgroups (Figure 3).

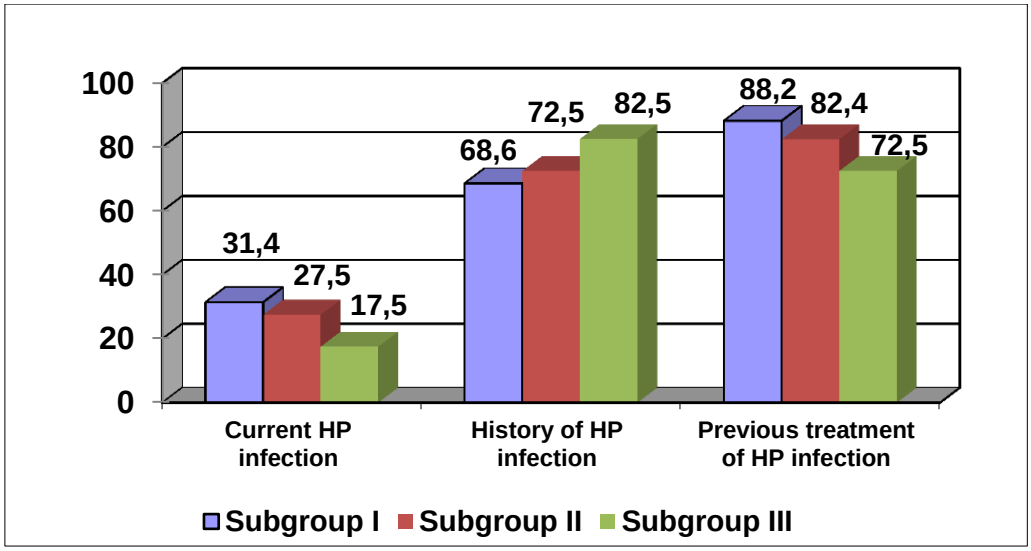


Figure 3. *Frequency (%) of HP infection and treatment of HP infection in the background according to the study subgroup*

No statistically significant differences were found regarding the allegations of patients in the study subgroups. Epigastric pain reported 49 (96.1%) patients in study subgroup 1, 48 (94.1%) patients in study subgroup 2 and 40 (100.0%) patients in study subgroup 3. Meteorism recorded 26 (51.0%), 20 (39.2%) and 17 (42.5%) patients, heartburn –39 (76.5%), 41 (80.4%) and 33 (82, 5%) patients, feeling of postprandial fullness - 43 (84.3%), 48 (94.1%) and 36 (90.0%) patients, feeling of early satiety - 38 (74.5%), 35 (68.6%) and 28 (70.0%) patients, respectively.

The frequency, severity and number of symptoms mentioned were also similar in patients in all 3 study subgroups. However, in study subgroup 3, compared to the other 2 study subgroups, none of the patients mentioned the presence of one or two symptoms.

Medications to alleviate the above-mentioned charges were administered by 47 (92.2%) patients in study subgroup 1, 41 (80.4%) patients in study subgroup 2 and 34 (85.0%) patients in subgroup 3 study. Proton pump inhibitors administered 33 (70.2%) patients in study subgroup 1, 34 (82.9%) patients in study subgroup 2 and 26 (76.5%) patients in study subgroup 3. study, H2-blockers - 2 (4.3%), 0 (0%) and 0 (0%) patients, both preparations - 12 (25.5%), 7 (17.1%) and 8 (23, 5%) patients, respectively.

Depending on the frequency, 10 (21.3%) patients in study subgroup 1, 10 (24.4%) patients in study subgroup 2 and 4 (11.8%) patients in study subgroup 3 administered the remedies once a week, respectively, 7 (14.9%), 16 (39.0%) and 12 (35.3%) patients - twice a week, 23 (48.9%), 10 (24.4 %) and 13 (38.2%) patients - 3 times a week, 7 (14.9%), 5 (12.2%) and 5 (14.7%) patients - 4 or more times a week.

According to the patients, the preparation was most effective in 8 (17.0%) people in study subgroup 1, in 11 (26.8%) people in study subgroup 2 and in 8 (23.5%) people in subgroup 3 study, partially effective - in 32 (68.1%), 29 (70.7%) and 17 (50.0%) people, inefficient - in 7 (14.9%), 1 (2.4%) and 9 (26.5%) people, respectively.

Treatment (frequency and duration of drug administration) were similar in all 3 study subgroups. Only the inefficiency of the remedy used was statistically significantly higher in patients in study subgroup 3, compared to patients in study subgroup 2 (26.5% and 2.4%, respectively; $p<0.01$).

Therefore, the comparative analysis of socio-demographic characteristics, risk factors, allegations, status of Helicobacter pylori infection and treatment for the eradication of HP infection did not find significant associations with the morphological severity of CAG in most cases.

The assessment of clinical features in people with CAG found the presence of the main symptoms in all patients in all 3 study subgroups. The frequency, severity and number of symptoms mentioned were also similar in patients in all study subgroups. The majority of patients in study subgroup 1 (92.1%) and study subgroup 2 (90.2%) and all patients in study subgroup 3 (100.0%) had 3-5 gastrointestinal symptoms. Data that suggested that patients with CAG and GED present a severe state of severity, compared to patients in the other 2 study subgroups: severe clinical picture, high frequency of ineffectiveness of treatment administered, clear associations with risk factors.

The comparative analysis of the prevalence of GMA forms, determined according to the Kimura-Takemoto endoscopic classification, found that the mild form of GMA was statistically significant with a higher frequency in study subgroup 1 (54.9% and 2.5%, respectively; $p<0.001$) and in study subgroup 2 (37.3% and 2.5%, respectively; $p<0.001$), compared to study subgroup 3. The moderate form of GMA was statistically significant with a higher frequency in study subgroup 3, compared to study subgroup 1 (82.5% and 2.5%, respectively; $p <0.001$) and study subgroup 2 (82.5% and 56.9%, respectively; $p<0.01$), the severe form of GMA was similar in all 3 study subgroups (Table 3).

Table 3. **Frequency of CAG forms by Kimura-Takemoto in the study subgroups**

Form of CAG (Kimura-Takemoto)	**CAG without IM and without GED (1)**		**CAG with IM (2)**		**CAG with GED (3)**		**p**
	abs.	**%**	**abs.**	**%**	**abs.**	**%**	
Mild (C1-C2)	28	54,9	19	37,3	1	2,5	1-3***, 2-3***
Moderate(C3-O1)	17	33,3	29	56,9	33	82,5	1-3***, 2-3**
Severe (O2-O3)	6	11,8	3	5,9	6	15,0	NS

Note: *statistically significant differences ** - p<0.01, *** - p<0.001*

The evaluation of the preponderance of OLGA system stages in patients in the study subgroups established that OLGA stage I was statistically significant with a higher frequency in study subgroup 1, compared to study subgroup 3 (29.4% and 2.5%, respectively; p <0.001), and stage II OLGA - in study subgroup 1 (41.2% and 7.5%, respectively; p <0.001) and in study subgroup 2 (58.8% and 7.5%, respectively; p <0.01), compared to study subgroup 3. OLGA stage III was statistically significant with a higher frequency in study subgroup 3, compared to study subgroup 1 (70.0% and 27.5%, respectively; p <0.001) and study subgroup 2 (70, 0% and 27.5%, respectively; p <0.01), and stage IV OLGA - in study subgroup 3, compared to study subgroup 1 (20.0% and 2.0%, respectively; p<0.01) and with study subgroup 2 (20.0% and 0%, respectively; p<0.01) (table 4).

Table 4. **Frequency of OLGA stages in the study subgroups**

OLGA stage	**CAG without IM and without GED (1)**		**CAG with IM (2)**		**CAG with GED (3)**		**Total**		**p**
	abs.	**%**	**abs.**	**%**	**abs.**	**%**	**abs.**	**%**	
I	15	29,4	7	13,7	1	2,5	23	16,2	1-3***
II	21	41,2	30	58,8	3	7,5	54	38,0	1-3***, 2-3**
III	14	27,5	14	27,5	28	70,0	56	39,4	1-3***, 2-3**
IV	1	2,0	0	0	8	20,0	9	6,4	1-3**, 2-3**

Note: *statistically significant differences ** - p<0.01, *** - p<0.001*

The analysis of the correlation between the severity of the morphological damage of the gastric mucosa in CAG and the GMA and IM stage, established according to the OLGA and OLGIM staging systems, confirmed that concomitant with the association of IM and GED increases the severity of OLGA and OLGIM stages. There is a direct (positive) association, of medium intensity and statistically significant between CAG forms and OLGA stages (ρ=0.49, p<0.001), a direct, strong and statistically significant association between CAG forms and OLGIM stages (ρ=0.85, p<0.001).

Table 5. **Correlation between OLGA system and Kimura-Takemoto classification in CAG**

Form of CAG (Kimura-Takemoto)	**OLGA stage**							
	I		**II**		**III**		**IV**	
	abs.	**%**	**abs.**	**%**	**abs.**	**%**	**abs.**	**%**
Mild (C1-C2)	19	39,6	27	56,3	2	4,2	0	0
Moderate(C3-O1)	4	5,1	24	30,4	44	55,7	7	8,9
Severe (O2-O3)	0	0	3	20,0	10	66,7	2	13,3

Analysis of the correlation between the severity of gastric mucosa damage according to the Kimura-Takemoto classification in CAG, determined endoscopically, and GMA and IM stage, established according to OLGA and OLGIM staging systems, found that concomitant with increasing CAG severity increases the severity of OLGA stages (Table 5) and severity of OLGIM stages (Table 6). There is a direct (positive) association, of medium intensity and statistically significant between CAG forms and OLGA stages (ρ=0.62, p<0.001), a direct, medium intensity and statistically significant association between CAG forms and OLGIM stages (ρ=0.33, p<0.001).

Table 6. **Correlation between OLGIM system and Kimura-Takemoto classification in CAG**

Form of CAG (Kimura-Takemoto)	OLGIM stage									
	0		I		II		III		IV	
	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
Mild (C1-C2)	28	58,3	13	27,1	7	14,6	0	0	0	0
Moderate(C3-O1)	18	22,8	15	19,0	34	43,0	9	11,4	3	3,8
Severe (O2-O3)	6	40,0	2	13,3	7	46,7	0	0	0	0

The correlation analysis revealed a direct, low intensity and statistically significant association between PG-I and PG-II values ($\rho=0.27$, $p<0.01$), a direct, strong and statistically significant association between PG-I values. I and PGR ($\rho=0.74$, $p<0.001$), a direct association, of low intensity and statistically significant between the values of PG-II and PGR ($\rho=0.2$, $p<0.01$) and a direct association, of low intensity and statistically significant between PG-II and G-17 values ($\rho=0.13$, $p<0.05$).

Simultaneously with the morphological worsening of CAG, there is a significant decreasing trend of PG-I ($p<0.001$) and PGR ($p<0.001$) values, a significant progressive trend of nitric oxide (NO) values in blood serum ($p<0.001$) and NO in gastric juice ($p<0.001$). Comparing these divergences according to the study subgroup we found that the mean value of PG-I was statistically significantly higher in patients in study subgroup 1, compared to patients in study subgroup 2 (72.63 ± 3.5 μg / L and 60.80 ± 3.3 μg / L, respectively; $p<0.01$) and with patients in study subgroup 3 (72.63 ± 3.5 μg / L and 40.67 ± 2.3 μg / L , respectively; $p<0.001$), in patients in study subgroup 2, compared to patients in study subgroup 3 (60.80 ± 3.3 μg / L and 40.67 ± 2.3 μg/L, respectively; $p<0.001$) (Table 7). PG-I>70 μg/L was determined statistically significantly with a higher frequency in patients in study subgroup 1, compared to patients in study subgroup 2 (58.8% and 31.4%, respectively; $p<0.01$) and with patients in study subgroup 3 (58.8% and 5.0%, respectively; $p<0.001$), in patients in study subgroup 2, compared with patients in study subgroup 3 (31.4% and 5.0%, respectively; $p<0.001$).

Table 7. **Mean values of serological examination determined in the study subgroups**

Parametru	CAG fără IM și fără GED (1)	CAG cu IM (2)	CAG cu GED (3)	Total	p
PG-I (μg/L)	72,63±3,5	60,80±3,3	40,67±2,3	59,38±2,1	1-2** 1-3*** 2-3***
PG-II (μg/L)	14,06±0,9	15,08±0,6	14,98±0,4	14,69±0,4	
PGR	5,80±0,4	4,29±0,3	2,65±0,1	4,37±0,2	1-2*** 1-3*** 2-3***
G-17 (μg/L)	5,94±0,7	7,89±0,8	4,95±0,4	6,36±0,4	
NO in blood serum (μM/L)	59,24±0,8	67,83±0,7	84,45±1,3	69,43±1,0	1-2*** 1-3*** 2-3***
NO in gastric juice (μM/g.prot)	29,38±1,1	37,38±1,0	43,59±1,0	36,26±0,8	1-2*** 1-3*** 2-3***

Note: *statistically significant differences ** - p<0.01, *** - p<0.001*

An inverse, statistically significant association was determined between the morphological forms of CAG (subgroups in our study) and PG-I values (ρ=-0.52, $p<0.001$), an inverse, statistically significant correlation between CAG forms and PGR values (ρ=-0.64, $p<0.001$), a direct correlation, statistically significant between CAG forms and serum NO values (ρ=0.85, $p<0.001$), a direct correlation, of medium intensity and statistically significant between the forms CAG and NO values in gastric juice (ρ=0.65, $p<0.001$).

Therefore, the study of the relationship between morphological status and functional activity of the gastric mucosa by determining the concentration of serological markers found a statistically significant reduction in mean PG-I and PGR and a statistically significant increase in mean NO in blood serum and NO in gastric juice concomitant with aggravation of CAG, determined endoscopically and morphologically.

Therefore, the frequency of GMA diagnosis based on serological parameters depends on the morphological type of gastric lesion: it is reduced in patients with CAG, without MI and without GED, and increases simultaneously with the morphological worsening of CAG. A statistically significant and significant reduction of PG-I and PGR was determined, a statistically significant and significant increase of NO in blood serum and NO in gastric juice simultaneously with the increase of the stages of OLGA and OLGIM systems. GMA, determined based on serological parameters, is important for the non-invasive diagnosis and prognosis of CAG with MI and / or CAG with GED, conditions that represent significant risk factors for the development of GC.

4. SUMMARY OF THE RESULTS OBTAINED

The comparative analysis of socio-demographic characteristics, risk factors, allegations, HP infection and treatment for the eradication of HP infection did not find statistically significant differences in most cases. Only an insignificant prevalence of the mean age was observed at the same time as the morphological worsening of CAG and the following statistically significant differences. In study subgroup 1 there were fewer men (21.6% and 51.0%, respectively; $p<0.01$), more women (78.4% and 49.0%, respectively; $p<0.01$), more non-smokers (70.6% and 45.1%, respectively; $p<0.01$), compared to study subgroup 2, and more normal-weight people (68.6% and 32.5%, respectively; $p<0.01$), compared to study subgroup 3. In study subgroup 3, compared to the other 2 study subgroups, patients mentioned only 3-5 symptoms. The ineffectiveness of the remedy administered to relieve symptoms was statistically significantly higher in patients in study subgroup 3, compared to patients in study subgroup 2 (26.5% and 2.4%, respectively; $p<0.01$). Based on the present analysis, the need for additional studies to identify a specific symptomatic model for CAG is highlighted.

According to the results of a recent cross-sectional retrospective study conducted in Italy and published in 2018, which evaluated a group of 668 patients with a mean age of 57.8 ± 4.7 years and upper gastrointestinal symptoms, the clinical predictors of CAG with MI are over 55 years of age, current smoking, active HP infection and a feeling of postprandial fullness [42]. And in the present study, these factors are more common in patients in subgroup 2 (CAG and IM) and subgroup 3 (CAG and GED) of the study.

In the present study, the comparative analysis of the prevalence of GMA forms, determined according to the Kimura-Takemoto endoscopic classification, found that the mild form of GMA was statistically significant with a higher frequency in study subgroup 1 (54.9% and 2.5%,

respectively); p<0.001) and in study subgroup 2 (37.3% and 2.5%, respectively; p<0.001), compared to study subgroup 3. The moderate form of GMA was statistically significant with a higher frequency in study subgroup 3, compared with study subgroup 1 (82.5% and 2.5%, respectively; p<0.001) and study subgroup 2 (82.5% and 56.9%, respectively; p<0.01), and the severe form of GMA was similar in all 3 study subgroups.

The analysis of the OLGA system stages in the patients in the present study established that OLGA stage I had a higher frequency in study subgroup 1, compared to study subgroup 3 (29.4% and 2.5%, respectively; p<0.001), and OLGA stage II - in study subgroup 1 (41.2% and 7.5%, respectively; p<0.001) and in study subgroup 2 (58.8% and 7.5%, respectively; p<0.01), compared to study subgroup 3. Stage III OLGA was statistically significant with a prevalent frequency in study subgroup 3, compared to study subgroup 1 (70.0% and 27.5%, respectively; p<0.001) and study subgroup 2 (70.0 % and 27.5%, respectively; p <0.01), and stage IV OLGA - in study subgroup 3, compared to study subgroup 1 (20.0% and 2.0%, respectively; p<0.01) and with study subgroup 2 (20.0% and 0%, respectively; p<0.01).

In the current cohort of 142 patients with CAG, OLGA stages I and II were determined in 54.2% of cases, and OLGA stages III and IV - in 45.8% of cases. A recent case-control study, based on histopathological data, found OLGA stages 0-II in 87.7% of cases and OLGA stages III and IV - in 12.3% of cases [28]. The higher frequency of patients with OLGA stages III and IV in the present study is determined by the serious health status of hospitalized patients.

The finding that most cases of GED (36 - 90.0%) were found in patients with OLGA stages III and IV and 4 (10%) were in OLGA stage I and II coincides with the results of the aforementioned study (90.0% and 10.0%, respectively). The determination of GED in 4 of 77 (5.2%) patients with OLGA I and II in the present study requires further investigation, as it is considered that this group of patients traditionally does not require prospective surveillance with ESU [28]. The analysis of the distribution of the stages of the OLGIM system noticed statistically significant differences in 2 cases: stage 0 OLGIM was statistically significant with a higher frequency in study subgroup 1, compared to study subgroup 3 (100.0% and 2.5%, respectively; p<0.001), and stage I OLGIM - in study subgroup 2, compared to study subgroup 3 (51.0% and 10.0%, respectively; p<0.001).

In the present study we found a direct correlation between the severity of gastric mucosa damage in CAG, determined endoscopically, and GMA and IM stage, established according to the OLGA and OLGIM staging systems, found that concomitant with increasing CAG severity increases the severity of OLGA and OLGIM stages. There is a direct (positive) correlation, of medium intensity and statistically significant between CAG forms and OLGA stages (ρ=0.62, p<0.001), a direct correlation, of medium intensity and statistically significant between CAG forms and OLGIM stages (ρ=0.33, p<0.001).

Therefore, CAG, according to the Kimura-Takemoto classification, correlates well with morphological CAG (the subgroups in the given study), OLGA system and OLGIM system. Several cohort studies have found that moderate-severe CAG (Kimura-Takemoto) is significantly associated with the presence of advanced precancerous gastric lesions and GC, as well as with the development of GC [34].

Comparative examination of OLGA stages with OLGIM stages in the general group of the present study found that the vast majority of cases with low risk of developing GC according to the OLGA system (98.7%) coincided with cases with low risk of developing GC according to

OLGIM system. Only 1 case (1.3%) with a low risk of developing GC according to the OLGA system was classified as a case with a high risk of developing GC according to the OLGIM system. Only 16.9% of the cases with high risk of developing GC according to the OLGA system coincided with the cases with high risk of developing GC according to the OLGIM system, and 83.1% of the cases with high risk of developing GC according to the OLGA system were classified as low-risk cases of GC development according to the OLGIM system. The $\chi 2$ Mantel-Haenszel test indicates a strong and statistically significant link ($\chi 2=24.51$, $p<0.001$) between the results of the OLGA system and the results of the OLGIM system. The downgrade of high-risk OLGA stages to lower-risk OLGIM stages has been noted in other studies. For this reason, the assessment of gastric mucosal changes should include the overall assessment of mucosal atrophy [36], and in patients with low OLGA, MI should be considered as a high risk marker for GC [35].

In the current cohort of 142 patients with CAG, HP was diagnosed in 37 (26.1%) cases by the morphological method and in 37 (26.1%) cases by the urease test, and HP-IgG was determined in 39 (27.5%) cases. Although significant differences in the detection of HP by these methods depending on the study subgroup were not found, a tendency to reduce the determination of these parameters was found simultaneously with the morphological worsening of CAG.

The correlation analysis was inversely proportional, of medium intensity and statistically significant between the CAG forms, determined by histological examination, and the PG-I values ($\rho=-0.52$, $p<0.001$), an inversely proportional correlation, of medium intensity and statistically significant correlation between CAG forms and PGR values ($\rho=-0.64$, $p<0.001$), a directly proportional, strong and statistically significant correlation between CAG forms and serum NO values ($\rho=0.85$, $p<0.001$), directly proportional, medium intensity and statistically significant correlation between CAG forms and NO values in gastric juice ($\rho=0.65$, $p<0.001$).

Simultaneously with the atrophy of the mucous glands in the antrum and / or the gastric body, the levels of PG-I and PG-II change accordingly and result in a decrease in PGR [14, 39]. It was found that PGR is closely correlated with histological CAG, and PGR<3.0 is considered an optimal value for the diagnosis of CAG with high sensitivity (71%), specificity (86%) and GMA detection accuracy (85%) [39]. PG-I and PGR levels decrease significantly in patients with CAG [25] in direct proportion to the extent of GMA, and correlate with histological outcomes [25] and endoscopic Kimura-Takemoto classification [31]. In addition, low serum PG-I levels and low PGR correlate with the severity of GMA and the association of early gastric neoplasms, thus suggesting that these parameters are sensitive biomarkers of gastric precancerous lesions and early GC [11].

Therefore, the use of serum biomarkers offers new possibilities in diagnosing premalignant gastric lesions (CAG, IM and GED) and in assessing the risk of GC, presents a sorting solution to UDE with biopsy and histopathological examination. Existing clinical practice has confirmed that "serological biopsy" of the gastric mucosa can be an objective information base for the screening, diagnosis and treatment of gastric diseases. The method can be used to perform prior screening of the population with screening patients for UDE and targeting indications for gastric mucosa biopsy in the population at high risk of GC [16, 22].

Based on the analysis of data from the literature [9, 14, 33] and the results of the present study, we developed an algorithm for diagnosis and surveillance of patients with CAG (Figure 4).

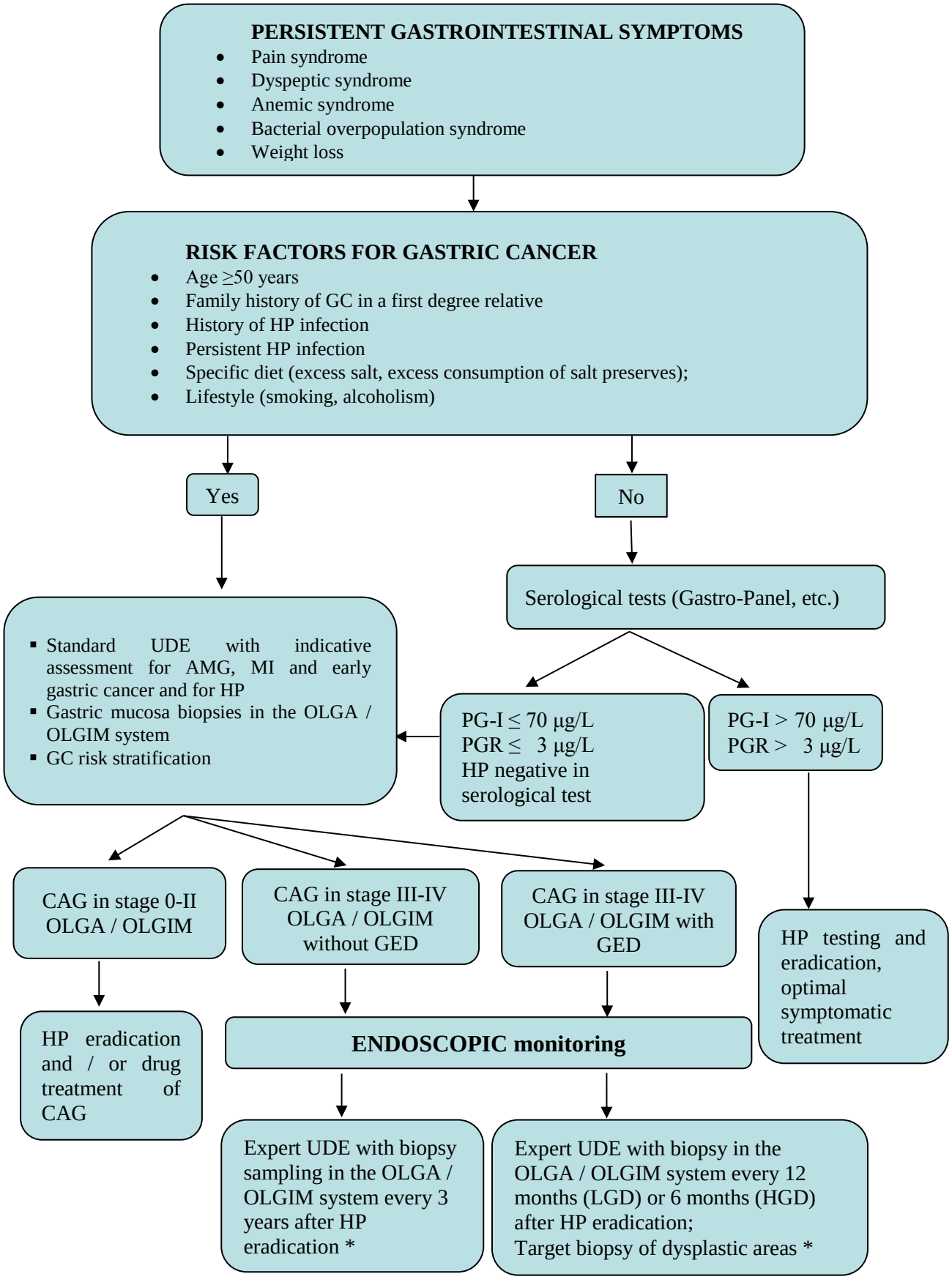


Figure 4. **Diagnostic and dynamic surveillance algorithm of patients with chronic atrophic gastritis (* MAPS I 2012, MAPS II 2019 [14, 33]).**

GENERAL CONCLUSIONS

1. The assessment of clinical features in people with chronic atrophic gastritis found the presence of the main symptoms in all patients in all 3 study subgroups. The frequency, severity and number of symptoms mentioned were also similar in patients in all study subgroups. Patients with chronic atrophic gastritis and dysplasia of the gastric epithelium, compared to patients in the other 2 study subgroups ($p<0.05$), have a more severe condition, with a more severe clinical picture and a higher frequency of treatment inefficiency administered.
2. The analysis of the correlation between the severity of gastric mucosal damage in chronic atrophic gastritis determined endoscopically with the stage of gastric mucosal atrophy and intestinal metaplasia, established histologically in the staging systems OLGA and OLGIM, found that with increasing severity of chronic atrophic gastritis in the OLGA system and the OLGIM system. A direct, moderate and statistically significant correlation was found between the forms of chronic atrophic gastritis and OLGA stages ($\rho=0.6$, $p<0.001$), a direct, weak and statistically significant correlation between the forms of chronic atrophic gastritis and OLGIM stages ($\rho=0.3$, $p<0.001$).
3. The diagnosis of gastric mucosal atrophy analyzed on the basis of serological test (pepsinogen I and II and PGI / II ratio) demonstrated statistically confirmed objectivity. The value of the serological test is represented by the non-invasiveness, simplicity and accessibility of the work and determines the primary role of the serological test to determine atrophy of the gastric mucosa as a first-line diagnostic method in patients with risk factors for gastric cancer.
4. The study of the relationship between morphological status and functional activity of the gastric mucosa, by determining the concentration of serological markers, found a statistically significant reduction in mean PG-I and PGR and a statistically significant increase in mean serum NO values and values averages of NO in gastric juice concomitantly with the morphological aggravation of the degree of atrophy of the gastric mucosa found endoscopically and histologically.
5. Based on the study, an algorithm for diagnosis and surveillance of patients with chronic atrophic gastritis was developed, approved and recommended for implementation in clinical practice.

PRACTICAL RECOMMENDATIONS

1. Serological testing is recommended as a first-line diagnostic method for patients with risk factors for chronic atrophic gastritis and gastric cancer.
2. Patients with positive serological test for chronic atrophic gastritis, associated with risk factors for atrophic gastritis and gastric cancer, patients after standard endoscopic examination, with or without stigmas for gastric mucosal atrophy, associated with positive serological test for chronic atrophic gastritis , requires endoscopic evaluation at expert level with mapped evaluation of the foveolar and vascular pattern of the gastric mucosa, methodical biopsy in OLGA and OLGIM system, and target biopsy of areas with endoscopic stigmas for mild gastric epithelial dysplasia, gastric epithelial dysplasia of severe degree and early neoplasms.
3. Methodological endoscopic and histological monitoring, with mapped imaging documentation, is recommended for chronic atrophic gastritis and for intestinal metaplasia on the background of atrophy of the gastric mucosa.

4. Early neoplasms and foci of dysplasia on the background of atrophic gastric mucosa require histological confirmation and interventional endoscopic treatment.
5. Consistent with the serological test, it is recommended to determine the antibodies and antigens for HP, and during the endoscopic examination - to perform the rapid urease test for HP, the presence of which is recommended to determine the histological evaluation of gastric mucosa biopsies.

SELECTIVE BIBLIOGRAPHY

1.Adamu M., Weck M., Gao L., Brenner H. Incidence of chronic atrophic gastritis: systematic review and meta-analysis of follow-up studies. *Eur J EpideIMol.* 2010; 25(7): 439-448.

2.Adamu M., Weck M., Rothenbacher D., Brenner H. Incidence and risk factors for the development of chronic atrophic gastritis: five year follow-up of a population-based cohort study. *Int J Cancer.* 2011; 128(7): 1652-1658.

3.Al-Nuaimya W.M., Faisalb H.M. Endoscopical and Histopathological Interpretation of Gastritis in Nineveh Province. *Ann Coll Med Mosul.* 2019; 41(1): 28-35.

4.Amal H., Leja M., Funka K., Skapars R., Sivins A., Ancans G. et al. Detection of precancerous gastric lesions and gastric cancer through exhaled breath. *Gut.* 2016; 65(3): 400-407.

5.Ang T., Pittayanon R., Lau J., Rerknimitr R., Ho S., Singh R. et al. A multicenter randoIMzed comparison between high-definition white light endoscopy and narrow band imaging for detection of gastric lesions. *Eur J Gastroenterol Hepatol.* 2015; 27(12): 1473-1478.

6.Antoš D., Enders G., Rieder G., Stolte M., Bayerdörffer E., Hatz R. Inducible nitric oxide synthase expression before and after eradication of Helicobacter pylori in different forms of gastritis. FEMS Immunol. *Med. IMcrobiol.* 2001; 30(2): 127-131.

7.Bang C.S., Lee J.J., Baik G.H. Diagnostic performance of serum pepsinogen assay for the prediction of atrophic gastritis and gastric neoplasms: Protocol for a systematic review and meta-analysis. *Medicine (Baltimore).* 2019; 98(4): e14240.

8.Bang C.S., Lee J.J., Baik G.H. Prediction of Chronic Atrophic Gastritis and Gastric Neoplasms by Serum Pepsinogen Assay: A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy. *J Clin Med.* 2019; 8(5): E657.

9.Banks M., Graham D., Jansen M., Gotoda T., Coda S., di Pietro M. et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. *Gut.* 2019; 68(9): 1545-1575.

10.Bodrug N., **Botezatu A**., Antonova N., Luca E., Botnari C., Branişte C. et al. Rolul clasificării OLGA în gastrita cronică atrofică. *Info-Med.* 2016; (2): 49-52.

11.Cha J.H., Jang J.S. Clinical correlation between serum pepsinogen level and gastric atrophy in gastric neoplasm. *Korean J Intern Med.* 2020; 35(3): 550-558.

12.Cheung K.S., Leung W.K. Risk of gastric cancer development after eradication of Helicobacter pylori. *World J Gastrointest Oncol.* 2018; 10(5): 115-123.

13.Crafa P., Russo M., Miraglia C., Barchi A., Moccia F., Nouvenne A. et al. From Sidney to OLGA: an overview of atrophic gastritis. *Acta Biomed.* 2018; 89(8-S): 93-99.

14.Dinis-Ribeiro M., Areia M., de Vries A., Marcos-Pinto R., Monteiro-Soares M., O'Connor A. et al. Management of precancerous conditions and lesions in the stomach

(MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). *Endoscopy*. 2012; 44(1): 74-94.

15. Domșa T., Gheban D., Rădulescu A., Borzan C. Cercetări preliminare privind infecția cu Helicobacter pylori la copii spitalizați proveniți din Nord-Vestul României. *J.M.B.* 2018; (1): 32-37.
16. Dong Z., Zhang X., Chen X., Zhang J. Significance of Serological Gastric Biopsy in Different Gastric Mucosal Lesions: an Observational Study. *Clin Lab.* 2019. Disponibil la: https://www.clin-lab-publications.com/eaop/download/3072 [accesat la 27.06.2020].
17. Friptuleac G., Bodrug N. Sănătatea ocupațională în programele de învățământ medical din Republica Moldova. *Revista Română de Medicina Muncii.* 2016; 67(1-2): p. 43-44.
18. Gawron A., Shah S., Altayar O., Davitkov P., Morgan D., Turner K. et al. AGA Technical Review on Gastric Intestinal Metaplasia-Natural History and Clinical Outcomes. *Gastroenterology.* 2020; 158(3): 705-731.
19. Ghidirim G., Misin I., Bodrug N., Istrati V. Fundamentare morfologică a tehnicilor contemporane de endoscopie digestivă avansată a joncțiunii esofago-gastrice. *Archives of the Balcan Medical Union.* 2016; 51: p. 20-28.
20. Hall S.N., Appelman H.D. Autoimmune Gastritis. *Arch Pathol Lab Med.* 2019; 143(11): 1327-1331.
21. Kim D., Chung W. Accuracy of Endoscopic Diagnosis of Mild Atrophic Gastritis with Helicobacter pylori Infection. *Clin Endosc.* 2018; 51(4): 310-312.
22. Kotelevets S.M., Chekh S.A. Serological Criteria for Mild, Moderate and Severe Atrophy in Atrophic Gastritis. *Biol Med.* 2015; 7(3): 1000235.
23. Lahner E., Carabotti M., Annibale B. Treatment of Helicobacter pylori infection in atrophic gastritis. *World J Gastroenterol.* 2018; 24(22): 2373-2380.
24. Lahner E., Gianluca E., Galli G., Annibale B. Atrophic gastritis and pre-malignant gastric lesions. *Transl Gastrointest Cancer.* 2015; 4(4): 272-281.
25. Lee J., Kim N., Lee H., Oh J., Kwon Y., Choi Y. et al. Correlations among endoscopic, histologic and serologic diagnoses for the assessment of atrophic gastritis. *J Cancer Prev.* 2014; 19(1): 47-55.
26. Lee S.Y. Endoscopic gastritis, serum pepsinogen assay, and Helicobacter pylori infection. *Korean J Intern Med.* 2016; 31(5): 835-844.
27. Marques-Silva L., Areia M., Elvas L., Dinis-Ribeiro M. Prevalence of gastric precancerous conditions: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2014; 26(4): 378-387.
28. Martínez D., Otero W., Ricaurte O. A Case and Control Study of the OLGA System's Impact on Detection of Chronic Atrophic Gastritis in Colombia. *Rev Col Gastroenterol.* 2016; 31(4): 358-364.
29. Mezmale L., Isajevs S., Bogdanova I., Polaka I., Krigere A., Rudzite D. et al. Prevalence of Atrophic Gastritis in Kazakhstan and the Accuracy of Pepsinogen Tests to Detect Gastric Mucosal Atrophy. *Asian Pac J Cancer Prev.* 2019; 20(12): 3825-3829.
30. Mihu I., Josan T. *Gastrita cronică la copil. Protocol clinic naţional.* Chişinău, 2017. 23 p.
31. Park Y., Kim N. Review of atrophic gastritis and intestinal metaplasia as a premalignant lesion of gastric cancer. *J Cancer Prev.* 2015; 20(1): 25-40.

32.Piciu A., Gheban D., Dumitrașcu D. Valoarea diagnostică și prognostică a clasificării ”OLGA” a gastritelor cronice. *Medicina Interna.* 2016; 13(1): 49-54.
33.Pimentel-Nunes P., Libânio D., Marcos-Pinto R., Areia M., Leja M., Esposito G. et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. *Endoscopy.* 2019; 51(4): 365-388.
34.Quach D., Hiyama T. Assessment of Endoscopic Gastric Atrophy according to the Kimura-Takemoto Classification and Its Potential Application in Daily Practice. *Clin Endosc.* 2019; 52(4): 321-327.
35.Quach D., Le H., Hiyama T., Nguyen O., Nguyen T., Uemura N. Relationship between endoscopic and histologic gastric atrophy and intestinal metaplasia. *Helicobacter.* 2013; 18(2): 151-157.
36.Rugge M., Fassan M., Pizzi M., Farinati F., Sturniolo G., Plebani M. et al. Operative link for gastritis assessment vs operative link on intestinal metaplasia assessment. *World J Gastroenterol.* 2011; 17(41): 4596-4601.
37.Shichijo S., Hirata Y. Characteristics and predictors of gastric cancer after Helicobacter pylori eradication. *World J Gastroenterol.* 2018; 24(20): 2163-2172.
38.Shin S., Kim J., Chun J., Yoon Y., Park H. Chronic atrophic gastritis and intestinal metaplasia surrounding diffuse-type gastric cancer: Are they just bystanders in the process of carcinogenesis? *PLoS One.* 2019; 14(12): e0226427.
39.Su W., Zhou B., Qin G., Chen Z., Geng X., Chen X. et al. Low PG I/II ratio as a marker of atrophic gastritis: Association with nutritional and metabolic status in healthy people. *Medicine (Baltimore).* 2018; 97(20): e10820.
40.Syrjänen K. Serum Biomarker Panel (GastroPanel®) and Slow-Release L-cysteine (Acetium® Capsule): Rationale for the Primary Prevention of Gastric Cancer. *EC Gastroenterology and Digestive System.* 2017; 3(6): 172-192.
41.Syrjänen K., Eskelinen M., Peetsalu A., Sillakivi T., Sipponen P., Härkönen M. et al. GastroPanel® Biomarker Assay: The Most Comprehensive Test for Helicobacter pylori Infection and Its Clinical Sequelae. A Critical Review. *Anticancer Res.* 2019; 39(3): 1091-1104.
42.Watari J., Chen N., Amenta P., Fukui H., Oshima T., Tomita T. et al. Helicobacter pylori associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. *World J Gastroenterol.* 2014; 20(18): 5461-5473.
43.White J., Banks M. Identifying the pre-malignant stomach: from guidelines to practice. *Transl Gastroenterol Hepatol.* 2020. Disponibil la: http://tgh.amegroups.com/article/view/5866/pdf [accesat la 27.06.2020].
44.Yakirevich E., Resnick M. Pathology of gastric cancer and its precursor lesions. Gastroenterol *Clin North Am.* 2013; 42(2): 261-284.

INFORMATION REGARDING THE VALORIZATION OF RESEARCH RESULTS

LIST OF SCIENTIFIC PUBLICATIONS AND EVENTS at which the results of the researches for the doctoral thesis in medical sciences with the topic „**Clinical, serological and morphological manifestations at patients with chronic atrophic gastritis**" were presented

SCIENTIFIC WORKS

- **Articles in scientific journals abroad:**

✓ ***articles in ISI, SCOPUS and other international databases***

1. **Botezatu A.**, Bodrug N. Chronic atrophic gastritis: an update on diagnosis. In: *Medicine and Pharmacy Reports* [Internet]. 2 Nov.2020 [cited 8 Nov.2020];. Available from: https://medpharmareports.com/index.php/mpr/article/view/1887 DOI 10.15386/mpr-1887
2. **Botezatu A.**, Bodrug N., Istrate V., Scorpan A. Chronic atrophic gastritis - clinical-paraclinical correlations: cross-sectional study. In: *Scientific Collection «InterConf»*,(36): with the Proceedings of the 7th International Scientific and Practical Conference «Challenges in Science of Nowadays» (November 26-28, 2020) in Washington, USA; pp. 963-975. Available at: https://interconf.top. ISBN 979-1-293-10109-3 UDC 616.33-002.2: 616.33-006.6-091.8

✓ ***publications in foreign magazines reviewed***

3. **Ботезату А. Н.**, Барба Д. В., Антонова Н. И., Бодруг Н. И. Предраковые заболевания и рак желудка. In: *Университетский терапевтический вестник.* 2020; 2(1): 52-54. ISSN 2713-1912.
4. Истрати В. Ф., Калин Г. В., Скурту А. А., Мунтяну Д. И., Бодруг Н. И., **Ботезату А. Н.**, Скорпан А. П. Влияние висмута трикалия дицитрата на динамику стабильных метаболитов оксида азота у больных с гастроэзофагеальной рефлюксной болезнью. In: *Университетский терапевтический вестник.* 2020, 2(1): 58-59 ISSN 2713-1912.

- **Publications in accredited national scientific journals:**

✓ ***articles in category B magazines***

5. **Botezatu A.** Clasificarea gastritelor cronice: actualități și discuții. In: *Sănătate Publică, Economie şi Management în Medicină.* 2020; 4(86): 71-78 ISSN 1729-8687.
6. **Botezatu A.** Leziunile precanceroase gastrice : definiție, clasificare, epidemiologie In: *Sănătate Publică, Economie şi Management în Medicină.* 2020; 4(86): 79-84 ISSN 1729-8687.
7. **Botezatu A.**, Bodrug N., Istrate V. Precancerous gastric lesions: pathophysiology and symptomatology. In: *Mold Med J*. 2020; 63(5): 62-67. doi: 10.5281/zenodo.4018962.

✓ ***articles in category C magazines***

8. Bodrug N., **Botezatu A.,** Antonova N., Luca E., Botnari C., Braniște C., Spinu A. Rolul clasificării OLGA în gastrita cronica atrofică. In: *INFO-MED.* 2016; 2(28): 49-52. ISSN 1810-3936.

- **Abstracts / abstracts / theses in the works of international scientific conferences**

9. **Botezatu A.**, Bodrug N., Istrate V., Luca E., Barba D. Aspecte contemporane în gastrita cronică atrofică. Al XXXVI/lea Congres Naţional de Gastroenterologie, Hepatologie şi Endoscopie Digestivă. In: *Journal of gastrointestinal and liver diseases*. Cluj-Napoca, România, 2016, vol. 25, supliment 2, pp. 80-81. ISSN 2457-3876.
10. Luca E., Bodrug N., Istrate V., Barba D., **Botezatu A**. Vasele palisade – un reper endoscopic cert al joncțiunii esofago-gastrice. Al XXXVI/lea Congres Naţional de Gastroenterologie, Hepatologie şi Endoscopie Digestivă. In: *Journal of gastrointestinal and liver diseases*. Cluj-Napoca, România, 2016, vol. 25, supliment 2, pp.116-117. ISSN 2457-3876.
11. Istrate V., Bodrug N., Ungureanu S., Luca E., **Botezatu A**. Eficienţa endoscopiei de magnificaţie în complex cu cromoendoscopia pentru diagnosticarea esofagului Barrett. Al XXXVI/lea Congres Naţional de Gastroenterologie, Hepatologie şi Endoscopie Digestivă. In*: Journal of gastrointestinal and liver diseases.* Cluj-Napoca, România, 2016, vol. 25, supliment 2, pp.124-125. ISSN 2457-3876.
12. **Botezatu A.** Actualități în leziunile precanceroase gastrice. Al XXXVIII-lea Congres Naţional de Gastroenterologie, Hepatologie şi Endoscopie Digestivă. În: *JGLD*. Craiova, România, 2018, vol. 27, suppl. 2, p.113 ISSN 2457-3876.
13. **Botezatu A.** The impact of premalignant gastric lesions and the role of noninvasive diagnosis in the early detection of gastric cancer = Impactul leziunilor precanceroase gastrice și rolul diagnosticului non-invaziv al acestora în depistarea precoce a cancerului gastric. In: Congresul consacrat aniversării a 75-a de la fondarea USMF „Nicolae Testemițanu”, 21-23 octombrie 2020: Abstract book. Chișinău: [s. n.], 2020, p. 187.

- **Patents, registration certificates, materials at invention salons**

14. **Botezatu A.,** Istrate V., Barba D., Țurcanu Gh., Luca E., Ursu C., Zlatovcena A., Antonova N., Bodrug N. Metodă de diagnostic a stărilor precanceroase gastrice morfologic schimbate. Brevet de invenție S2020 0115. Data de depozit 2020.09.21.

- **Participări cu comunicări la foruri ştiinţifice:**

✓ **International**

15. **Botezatu A.**, Bodrug N. Aspecte contemporane în gastrita cronică atrofică, *Iaşi, 2016 Conferința anuală a Universității de Medicină și Farmacie din Iași ”Gr T.Popa” 04.03-06.03.2016.*
16. **Ботезату А.Н**., Истрати В.Н., Бодруг Н.И. (Молдова) «Предраковые заболевания и рак желудка» III Российский гастроэнтерологический конгресс с международным участием «ГАСТРОЭНТЕРОЛОГИЯ РОССИИ ОТ РОЖДЕНИЯ ДО СТАРОСТИ (педиатрические, терапевтические, хирургические и медико-социальные аспекты)», Санкт-Петербург, 29-30 октября 2020, Россия.

✓ **National**

17. **Botezatu Adriana** Gastrita cronică atrofică: specificul evoluției și a patternului foveolar la vârstnici. Zilele USMF ”Nicolae Testemițanu”, octombrie, 2017.
18. **Botezatu Adriana** Actualități în leziunile precanceroase gastrice, Chișinău, 24-25 octombrie 2017, Congresul III de Medicină Internă.
19. **Botezatu Adriana** Actualități în gastrita atrofică ca leziune precanceroasă gastrică. Zilele USMF ”Nicolae Testemițanu”, octombrie, 2018.
20. **Botezatu Adriana** Elucidarea manifestărilor clinice, serologice și morfologice la pacienții cu gastrita cronică atrofică. Zilele USMF ”Nicolae Testemițanu” octombrie, 2019.
21. **Botezatu Adriana** Impactul leziunilor precanceroase gastrice și rolul diagnosticului non-invaziv în depistarea precoce a cancerului gastric. Congres 75 ani a USMF ”Nicolae Testemițanu”, 21-23 octombrie, 2020.

- **Participation with posters in scientific forums:**

✓ **international**

22. Bodrug N., Istrate V., Scorpan A., **Botezatu A.** Chromoendoscopy with acetic acid in the diagnosis of Barrett esophagus Simpozionul Centenarul Medicinei Interne Românești. Cluj-Napoca, 24-26 octombrie 2019.
23. Bodrug N., Istrati V., Istrate V., **Botezatu A.** Identificarea leziunilor premaligne – un pas important în prevenirea cancerului gastric Simpozionul Centenarul Medicinei Interne Românești. Cluj-Napoca, 24-26 octombrie 2019.
24. Bodrug N., Botezatu A., Istrate V. Identifying prencancerous lesions – an important step in gastric cancer prevention. Reuniunea Societății Române de Neurogastroenterologie. Iași, 07-09 noiembrie 2019.

✓ **national**

25. **Botezatu Adriana**, Bodrug Nicolae Aspecte contemporane în gastrita cronică atrofică. Zilele USMF ”Nicolae Testemițanu”, octombrie 2017

BOTEZATU Adriana

CLINICAL, SEROLOGICAL AND MORPHOLOGICAL MANIFESTATIONS IN PATIENTS WITH CHRONIC ATROPHIC GASTRITIS

321.01 - INTERNAL DISEASES (GASTROENTEROLOGY, HEPATOLOGY)

Summary of the doctoral thesis in medical sciences

Approved for printing: 12.04.2021 Paper size 60x84 1/16

Offset paper. Digital printing. Circulation - 100 ex.

Printing sheets: 1.5 Order no. 223

"Sirius" printing house, Alexandru Lăpuşneanu street 2, Chisinau MD-2004