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Clinical and endoscopic features of post - nonsteroidal anti-inflammatory (NSAIDs) gastritis in elderly

– PhD thesis summary –

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CHAPTER 1. BACKGROUND AND OBJECTIVES

Gastrointestinal complications of non-steroidal anti-inflammatory drugs (NSAIDs) remains a major health problem, or a major cause of morbidity to NSAIDs, especially in elderly patients, despite great efforts over the past 20 years to find strategies to reduce their adverse effects. [1]

Mean age was identified as the most important risk factor for post-NSAID gastritis, acting as a risk factor that increases linearly. [2]

An increase life expectancy by about 5.5 years would be sufficient for a doubling of the incidence of gastrointestinal adverse effects of NSAIDs. [3]

The current trend to restructure human society on a planetary level is marked by three fundamental processes and simultaneous include: **globalization, urbanization, aging**. [4]

As a result of these trends the population restructuring plan, which gradually increases the number of elderly, there is an increase in the share of health problems specific to these age groups. According to medical health surveys in 1989 and 1997 and comparing their results, it shows a significant increase in weight in the general population types of pathology-specific aging population, a phenomenon explained by the aging population and increasing disease diagnosis. [5]

In terms of teaching stomach problems caused by NSAIDs can be classified as follows:

- Clinical manifestations (dyspepsia, pain)
- Changes in endoscopic and / or histological
- Gastric complications (bleeding, perforation, obstruction) [6]

NSAIDs, including aspirin, are among the most widely used drugs in the world. In a population study of the prevalence of weekly use of NSAIDs by elderly patients was 70% and 60% of aspirin. In the U.S. for example, approximately 13 million people use NSAIDs regularly. [7]

Every year 70 million prescriptions written and over 30 billion annually NSAIDs are sold as OTC (over the counter), so that the risk of side effects is greater. [8]

Unfortunately, although clinically effective, widespread use and ,sometimes, higher than recommended doses of these drugs , has led to an increased prevalence of gastrointestinal lesions (gastritis, ulcers, bleeding, perforation), at a rate of 2.5 -4.5% per year. [9, 10, 11] compared the frequency of severe gastrointestinal events in individuals not exposed to NSAIDs (0.1-0.3% per year).

Prevalence of gastric complications in patients taking NSAIDs is higher in certain risk groups [12], including:

• age> 65 years [13]
• patients with a history of peptic ulcer or gastrointestinal complications
• concomitant use of oral anticoagulants [14, 15]
• concomitant use of corticosteroid therapy and / or ASA [16]
• use of high doses of NSAIDs or NSAIDs combinations. [11]

In the context of discovery and underline the real extent of the problem -gastritis after NSAIDs in the elderly-, at least in the last 20 years, **the main objectives** of this study are:

- to establish the clinical and endoscopic aspects of NSAIDs-induced gastritis in the elderly and the correlations between them.
- to study the risk factors for NSAIDs gastritis (endoscopically diagnosed) in eldery

- to determine any histopathological features (in patients whom gastric biopsies were performed)

- to establish possible correlations between histological and endoscopic appearance of gastritis after NSAIDs in the elderly.

- to structure thesis results and generate discussion that will result in the following conclusions regarding the particularities of NSAIDs-induced gastritis in the elderly and to provide a new and differentiated approaching of the problem.

CHAPTER 2. MATERIALS AND METHODS

We conducted a retrospective observational study with data on a sample of 172 elderly patients diagnosed with NSAIDs-induced gastritis, admitted between September 2006 - September 2010 Medical Clinic 1 of Constanta County Emergency Hospital and the Hospital Clinic of Gastroenterology Constanta County Emergency.

Establishing the study group

Volume delineation of study sample was done by identifying 480 patients with endoscopic gastritis, of which 306 elderly patients (over 65 years) with gastritis, but only the 172 post NSAIDs gastritis were analyzed further.

Patients were monitored clinically and laboratory and diagnosis of gastritis post NSAIDs was determined by clinical examination in conjunction with upper digestive endoscopy (UDE), and by histopathological examination in some patients.

Etiology of post-NSAID gastritis was determined by highlighting the use of NSAIDs. Patients who used NSAIDs at least 14 days in any dose, with at least 3 months prior to endoscopy were considered consumers of NSAIDs.

Protocol exploration of patients

Data collection was done for each patient admitted to the mentioned range, ie clinical data, laboratory and endoscopic aspects and HP infection status and histopathological description (in a subset of 100 patients), information obtained from patient admission sheet.

Thus, the study group included 172 elderly patients and for each of them a personal record was done, which included:

• ***personal data:***

¬ name

¬ age

¬ gender

¬ medium of origin: urban / rural

• ***personal habits****:*

¬ alcohol consumption: never / occasionally / daily

¬ smoking: yes / no

¬ stress: absent / low / moderate / severe

For assessing stress, it was used the Perceived Stress Questionnaire, developed by Levenstein et al. (1993), which is a useful tool in determining the level of perceived stress. [17]

• ***complete diagnosis****:*

¬ underlying disease (gastritis post NSAIDs)

¬ osteoarthritis

¬ cardiovascular diseases (hypertension, coronary artery disease, heart failure)

¬ hepatopathy

¬ diabetes

¬ chronic Obstructive Pulmonary Disease

¬ chronic Renal Failure

¬ osteoporosis

¬ rheumatoid arthritis / ankylosing spondylitis

• ***Symptoms***:

- Uncomplicated

epigastric pain

nausea and vomiting

heartburn

bloating

- Complicated

haematemesis and melaena (UGB)

We considered a clinically significant bleeding episode, when the following conditions were present (listed in Baveno III consensus): [18]

signs of hypovolemia (systolic blood pressure <100 mm Hg or postural change> 20 mm Hg and / or pulse> 100/min on admission) required transfusion of ≥2 units of blood within 24 h and plasma required> 1000 ml in 24 h from time zero considered when admission to hospital.

• ***Laboratory data*** (recorded at the time of admission) - were required following determinations:

¬ complete blood count (to follow in particular the presence or absence of anemia)

¬ transaminases

¬ seric glucose

¬ creatinine

¬ inflammatory tests (ESR, fibrinogen, CRP)

• ***endoscopic examination*** (if some patients had multiple endoscopies performed first endoscopy endoscopy was used as indicator).

Endoscopies were performed by the classical method, after 6 hours of fasting, with a flexible fiber-optic endoscope attached to a cold light source flash under local anesthesia with xilocainǎ 10%. Iv sedation with midazolam was necessary in some patients.

Biopsies protocol:

Biopsy specimens were made with standard biopsy forceps: 2 in gastric antrum (front and rear) and 2 in the body, and additional biopsies of focal lesions detected endoscopically around. An antral specimen was used to test HP infection. [19]

Endoscopic information included:

-location, extent and number of lesions that were found

- type of endoscopic lesions: edema, exudate, erythema, erosion, hemorrhage (Sydney endoscopic classification) [20]

HP infection was determined in a subset of 121 patients, using a rapid urease test on gastric biopsy.

Rapid urease test was performed when endoscopic exploration and is based on the principle that HP produces large amounts of urease. Enzyme converts urea into ammonia and CO2, with a consequent increase in environmental pH.

Helicobacter pylori infection is normally considered present if the results are positive in at least two of three diagnostic tests (eg rapid urease test, histological examination and Helicobacter pylori IgG antigen). It should be noted however that in our study the only test available was rapid urease test, HP infection was considered present in patients with rapid urease test positive.

• ***histopathology***, is not a routine diagnostic method, that's why it was done only to a subset of 100 patients. Gastric biopsies obtained at endoscopy were analyzed in the Laboratory of Clinical Pathology Constanta County Emergency Hospital. For analysis of samples in optical microscopy, fixation of fragments was performed in 8% buffered formalin, then paraffin inclusion was made.

Paraffin sections (3-6) were done and staining was performed with hematoxylin-eosin (routine). All slides were examined for gastric mucosal injury. We note that Giemsa staining, to detect HP infection, wasn't performed.

• ***NSAID treatment and medication associated***- careful anamnesis about NSAID use (number of NSAIDs used, conventional or specific, dose used, the length of time , if the patient had gastric mucosal protective associated or not, association of NSAIDs with ASA, oral anticoagulants, corticosteroids). In conventional NSAID group (group I) we included non-selective NSAIDs and in newer NSAID group (group II) we have included selective NSAIDs and COX-2 specific inhibitors.

Associated medications (for other comorbidities) were thorough review, especially the gastrotoxic drugs (eg bisphosphonates, antihypertensive medication, antibiotics, corticosteroids, low-dose aspirin, oral anticoagulants ...).

For the investigation of the clinical and endoscopic NSAIDs-induced gastritis we monitored:

• the most common gastric signs and symptoms

• NSAIDs mostly used by elderly patients

• NSAIDs -induced gastritis correlation with HP infection

• the existence of predictive risk factors for post-NSAIDs gastritis complications in elderly patients (concomitant use of ASA, oral anticoagulants, corticosteroids, smoking, alcohol, stress, medication with gastric toxicity)

• how comorbidities affect post-NSAIDs gastritis in elderly

• how complications can influence associated diseases (cardiovascular, COPD, liver disease, diabetes, etc.).

Statistical analysis of data

Data from the study group were used to complete a database using SPSS v. 20.0, the same program was used and statistical data processing.

The data were collected in tables according to specific features. Data presentation was made by graphic type "column" or "sectoral" according to scientific requirements in the field.

Basal values of continuous quantitative variables were reported as mean and standard deviation and categorical variables were reported as number of patients (%).

To determine the distribution of parameters, a Shapiro-Wilk test was applied. According to this test, then, to compare variable intra-and inter-group were applied following tests: chi-square (chi-squared χ^2 test or Fisher), to compare intragroup of categorical variables and for quantitative variables tests Pearson and Spearman respectively, were used.

Moreover, a multivariate logistic regression analysis was used to identify predictors (risk) independent post NSAIDs gastritis.

Odds ratios (OR) and confidence interval (CI) were estimated where appropriate, considering a significance level of 95%.

Interpretation of tests: if the p-value (p-value) calculated by the software, is below 0.05, then there is association between correlated variables (null hypothesis is rejected). It is considered that a rate below 5 practically acceptable, is due to chance.

p value was calculated with the following statistical significance:

-p> 0.05 significant differences;

-p <0.05 significant differences;

-p <0.01 significant differences;

-p <0.001 highly significant differences.

Also descriptive analyzes were used to describe characteristics and crosstab study group.

CHAPTER 3. RESULTS AND DISCUSSIONS

Of the 480 patients diagnosed with gastritis were selected 306 elderly patients with endoscopic gastritis and subsequently were elected with chronic use of NSAIDs. Selected subgroup of this study included 172 patients. (Figure 1)

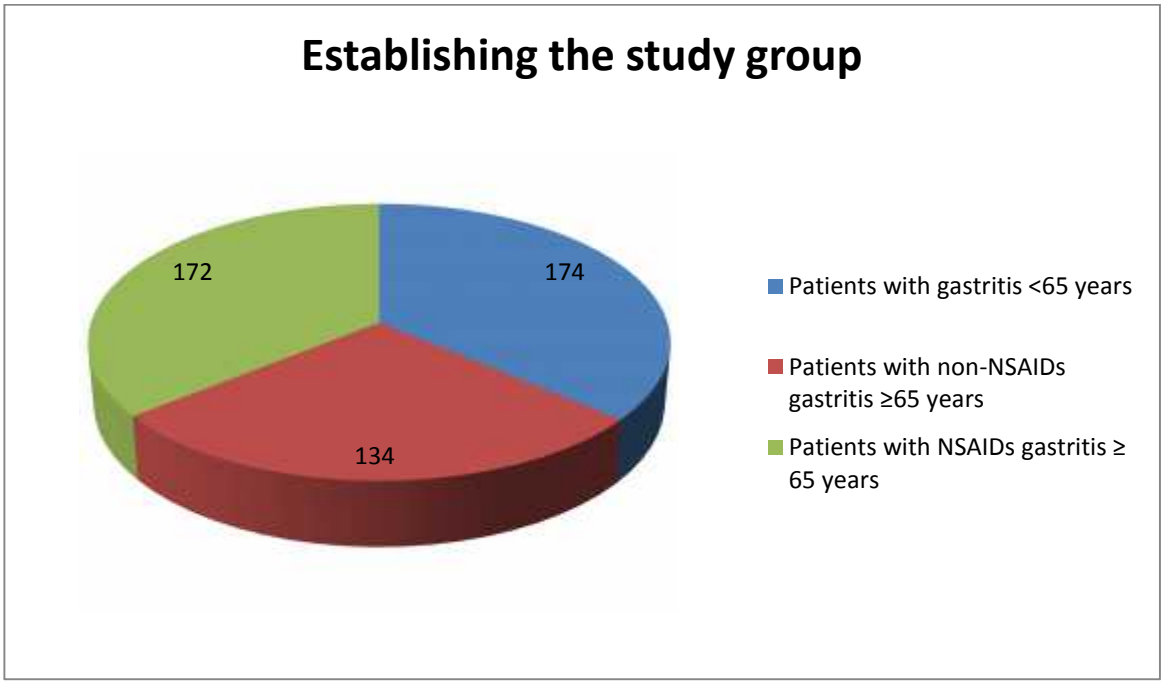


Figura 1. Establishing the study group

The first observation that could be made is that in the elderly, gastritis was almost two times more frequent than in patients under 65 years (63.75% vs. 36.24%).

In the group of patients over 65 years initially selected with endoscopic gastritis, gastritis prevalence of post NSAIDs was 56.21% (172 of 306 patients), consistent with the literature where it is estimated that 50-60% of elderly consumers of NSAIDs have endoscopic lesions of gastritis. [21]

3.1. DEMOGRAPHIC CHARACTERISTICS

Demographic characteristics of the study group are shown in Table 1.

Characteristics		Study group (n=172)
Males:Females		36:136
Medium of origin (urban:rural)		122:50
Mean age (average±sd)		75,98 (± 6,055)
Age groups	65-74 years	76
	75-84 years	76
	≥85 years	20

Table 1. Demographic characteristics of the study group

A.Distribution by gender

The study group included 172 patients, including 136 women and 36 men with a ratio F/M = 3.78/1.

Sex distribution was predominantly female (79.1% women vs. 20.9% men).

Although the 2009 census shows that the female population is slightly majoritary (51.2%) in our study benchmarking sex showed a predominantly affecting females (79.1%), which can be explained by higher addressing for women to health services. This might correlate with higher incidence of osteoarthritis (BAVP) and hence higher consumption of NSAIDs in women.

B. Distribution by age

Patients in the study group were aged between 65 and 90 years (with a mean age of 75.98 years ± 6.055).

Advanced age is considered an independent risk factor for primary and major gastrointestinal events. [22, 23, 24, 25, 26]

The average age of patients according to sex is shown in the figure below, noting that both men have similar values (76.25 years) and females (75.90 years) and compared with the average age of the entire group.

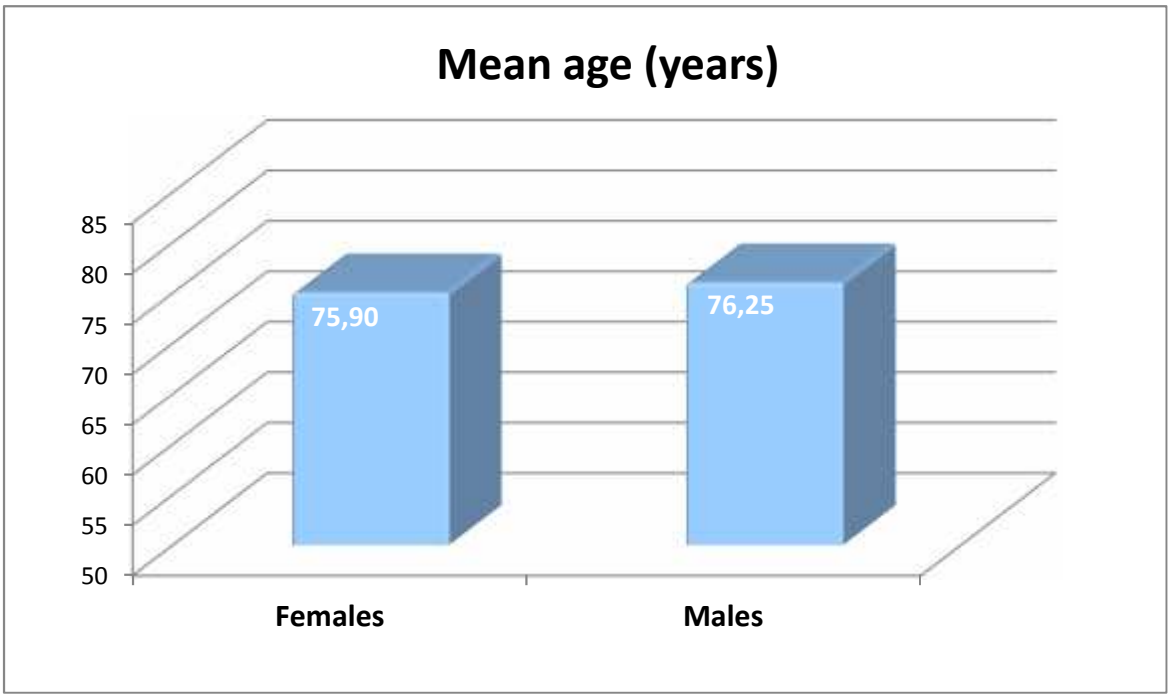


Figure 2. Distribution of mean age by gender

Distribution by age groups and by gender, shows predominance of females in all age groups, especially between 75-84 years (64 of 76 to 84.21%).

Although men are a minority in all age groups, the highest frequency of males was in the age group ≥85 years (6 of 20 patients, 30%) as seen in the chart below.

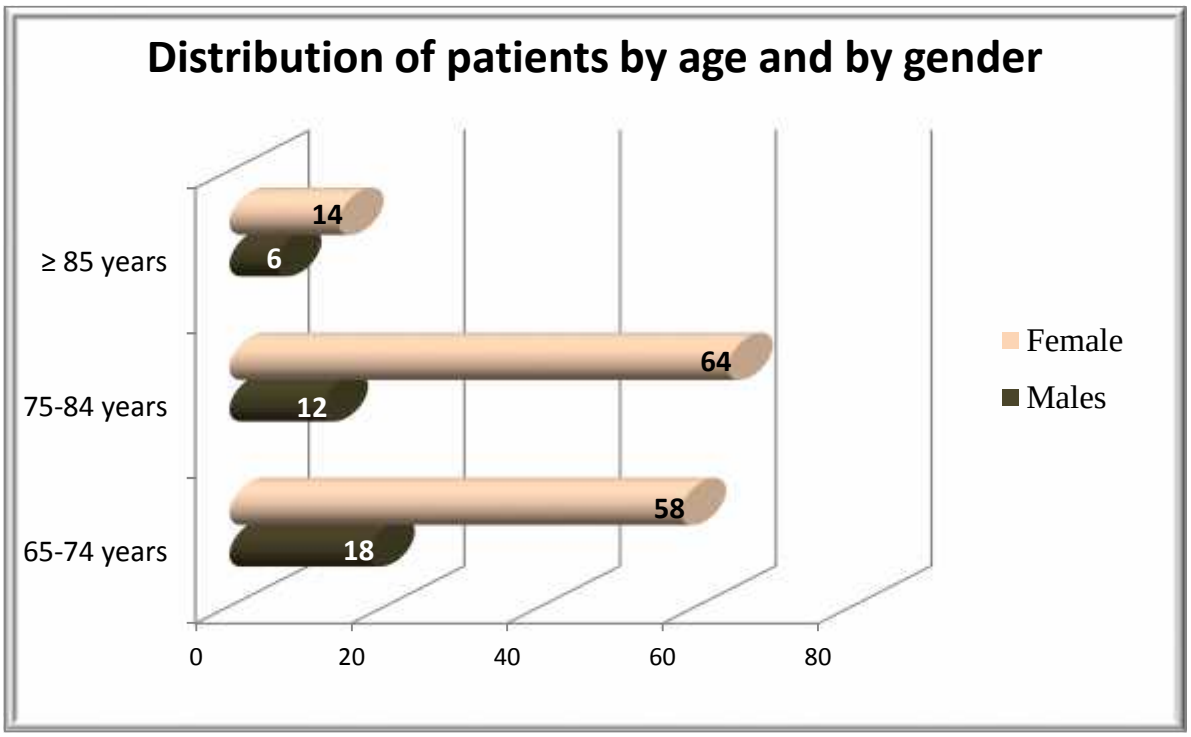


Figure 3. Distribution of patients by age and by gender

Regarding the study group we conclude that most patients had ages between 65 and 84 years (88.4%). Patients over 85 years accounted for only 11.6% of the entire group.

This should be seen also from the point of view of life expectancy in our country, estimated at 66.1 years for men and 73.99 years for women, the number of elderly "very elderly", over 85 years, being lower in the general population, not only in the study group. [27]

One important thing to note is that of the 20 patients over 85 years, 13 were in rural areas and only 7 of the urban areas, although overall there was a greater addressability of urban patients (122 versus 50 patients in rural areas). Explanation that addressing elderly "very elderly" was higher in rural areas (26%) than urban areas (5.73%) could be that most patients in rural areas (6) had onset complications (UGB), for that reason presentation to the doctor was necessary.

C. Medium of origin

In our country according to the latest census, the urban population is 55.2%, and 44.8% rural. [28]

However, in our study group, 122 patients (70.9%) were from urban areas and the remaining 50 patients (29.1%) in rural areas.

According to other studies, there is a preponderance of patients in urban areas, so of course explained by higher degree of medical information and health services addressing.

Currently restructuring of health services in rural areas is increasingly offering patients the possibility of investigation and even guidance to the hospital, especially in case of complications and emergencies.

The distribution of patients in the study group according to area of origin is shown below tabular and graphic.

Medium	Patients (no)	Percentage
Urban	122	70,9%
Rural	50	29,1%

Table 2 . Distribution of cases by medium of origin

Clear preponderance of urban patients in the study group could be explained by higher addressability to medical services and perhaps also by a higher medical education, although as mentioned above in case of serious medical problems (UGB, uncontrolled pain) may be greater addressability even in rural areas.

For example, in case of UGB addressing was 12% in rural areas (6 of 50 patients) and 4.91% in urban areas (6 of 122 patients).

3.2. BEHAVIOUR AND LIFESTYLE

Diet, alcohol consumption and smoking, as well as stress are possible risk factors for gastritis, there are many studies that have tried to establish a causal link between them and post NSAIDs gastritis. [29]

The table below shows the distribution of patients according to smoking, alcohol and stress.

		Yes	No
Smokers		98 (57%)	74 (43%)
Alcohol consumption		36 (20,9%)	136 (79,1%)
Stress	Low	15 (8,7%)	
	Moderate	45 (26,2%)	
	Severe	112 (65,1%)	

Table 3. Distribution of cases according to the behaviour and lifestyle

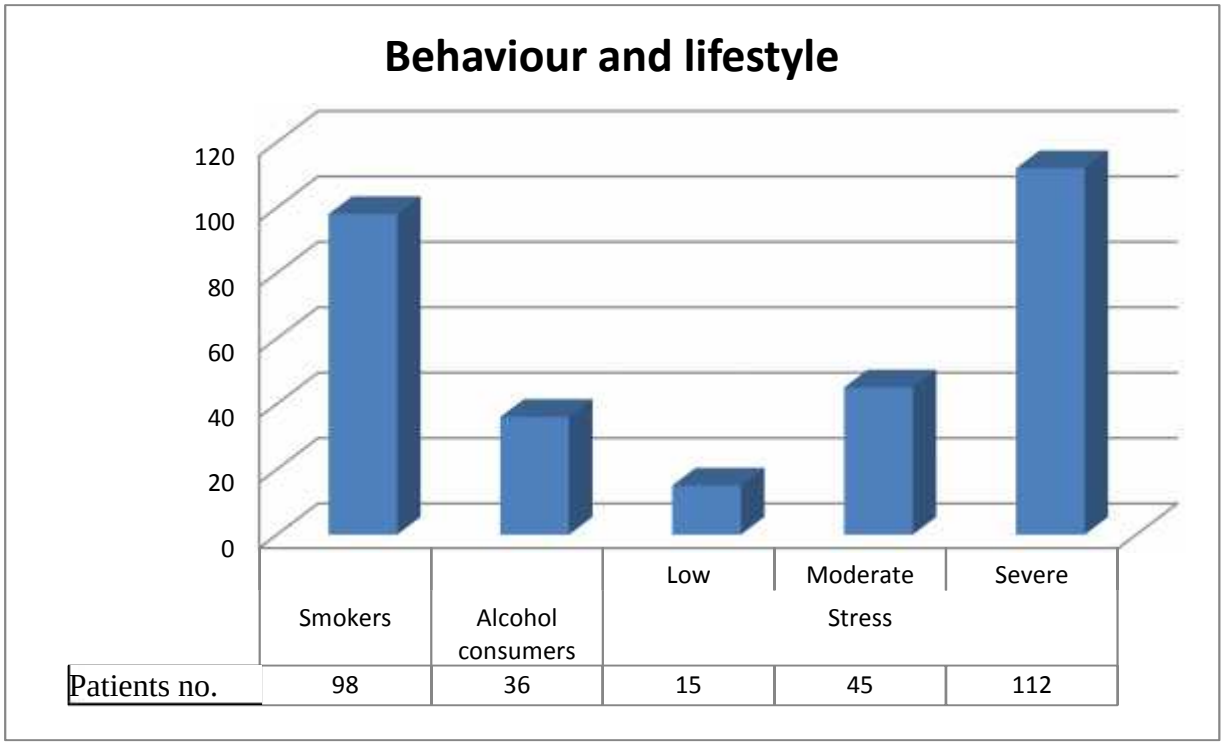


Figure 5. Behaviour and lifestyle

Regarding the smoking, its rate in the study group was significant (57%), while the rate of drinkers was low (20.9%), which could be explained by the fact that women prevailed in our study, overall alcohol consumption is most common in men. We also mention that stress was present in all patients.

A. Smoking

The Report of the Surgeon General's Report 1990 (USDHHS, 1990) [30], smoking was associated with gastric ulcers and erosions in three studies that included consumers of NSAIDs.

On the contrary, Aalykke and colleagues (1999) showed in a comparative study that smokers have higher risk of complications (UGB). [31] Also Weil found similar results (2000). [32]

Quitting smoking has beneficial effects on gastritis.

Data from observation charts of patients allowed their classification in categories smoker / non-smoker. Next we analyzed the distribution of these categories according to sex and age groups.

Over 50% (56.97%) patients of the study group were smokers, smoking is much more common in men - about 3 quarters of them (77.77%) than women - about half of them (51, 47%).

Smoking did not influence pain as a symptom of gastritis, but significantly influenced the occurrence of UGB, literature data confirming that the smoking is a possible risk factor for gastric complications from NSAIDs.

B. Alcohol consumption

Numerous studies indicate that an occasional consumption of alcohol does not increase the incidence of gastritis, but daily consumption of concentrated alcohol can lead to increased rates of complications (UGB), especially in patients who take aspirin while. [33]

Also, daily alcohol consumption associated with chronic use of NSAIDs increases the frequency of gastric complications, probably by synergistic mechanism of damage to the gastric mucosa. [34]

Distribution of patients according to the results of alcohol and sex are presented in the tables below.

Gender	**Alcohol consumption**		
	Never	Occasionally	Daily
Males	6(16,66%)	9(25%)	21(58,33%)
Females	130(95,58%)	6(4,41%)	0
Total	136	15	21
Percentage	79,06%	8,72%	12,20%

Table 4. Distribution of cases according to alcohol consumption and sex

Age groups	**Alcohol consumption**		
	Never	Occasionally	Daily
65-74 years	60 (78,94%)	7(9,21%)	9(11,84%)
75-84 years	62 (81,57%)	7 (9,21%)	7(9,21%)
≥85 years	14(70%)	1(5%)	5(25%)

Table 5. Distribution of cases according to alcohol consumption and age

Daily users of alcohol were predominantly men, the highest rate was found in the age group over 85 years.

Non-consumers of alcohol were mostly women and were found in high proportion (approximately 80%) in the age groups 65-74 years and 75-84 years.

Daily alcohol consumption was associated in our study with both pain and the presence of upper gastrointestinal bleeding. Of the 21 men daily consumers of alcohol, 17 had daily treatment with low dose aspirin. Of these, 4 patients had upper GI bleeding, ie 23.52%.

We note that in patients who have met accumulation of risk factors (chronic use of NSAIDs, the combination of low-dose aspirin and daily alcohol consumption) bleeding had higher frequency.

C. Stress

Psychological stress has long been considered very important risk factor for gastritis. Although there are insufficient data to support a causal link between mental stress and NSAIDs gastritis, further research might reveal other aspects. [17]

Stress evaluation in patients of the study group was performed using PSQ questionnaire (Perceived Stress Questionnaire).

Note that the psychotraumatic events,encountered in elderly patients in the study group, were:

-widowhood (lose of husband/wife)

-psychological stress associated to chronic diseases

-retirement

-chronic pain and disability

-family problems

All patients of the study group experienced some degree of stress.

On the whole lot was over 90% of cases (91.27%) with medium or severe stress.

Age groups	**Stres**		
	Low	Medium	Severe
65-74 years	10 (13,15%)	23 (30,26%)	43 (56,57%)
75-84 years	4(5,26%)	20 (26,31%)	52(68,42%)
≥85 years	1(5%)	2(10%)	17(75%)

Table 6. Distribution of cases according to the stress and age groups

In terms of stress , distribution of patients , according to age groups, has also met the predominance of severe stress at 65-74 years (56.57%) and the 75-84 years (68.42%) and over 85 years (75%).

This trend of linear increase in the percentage of severe stress with age might be explained through increased accumulation of psychotraumatic events.

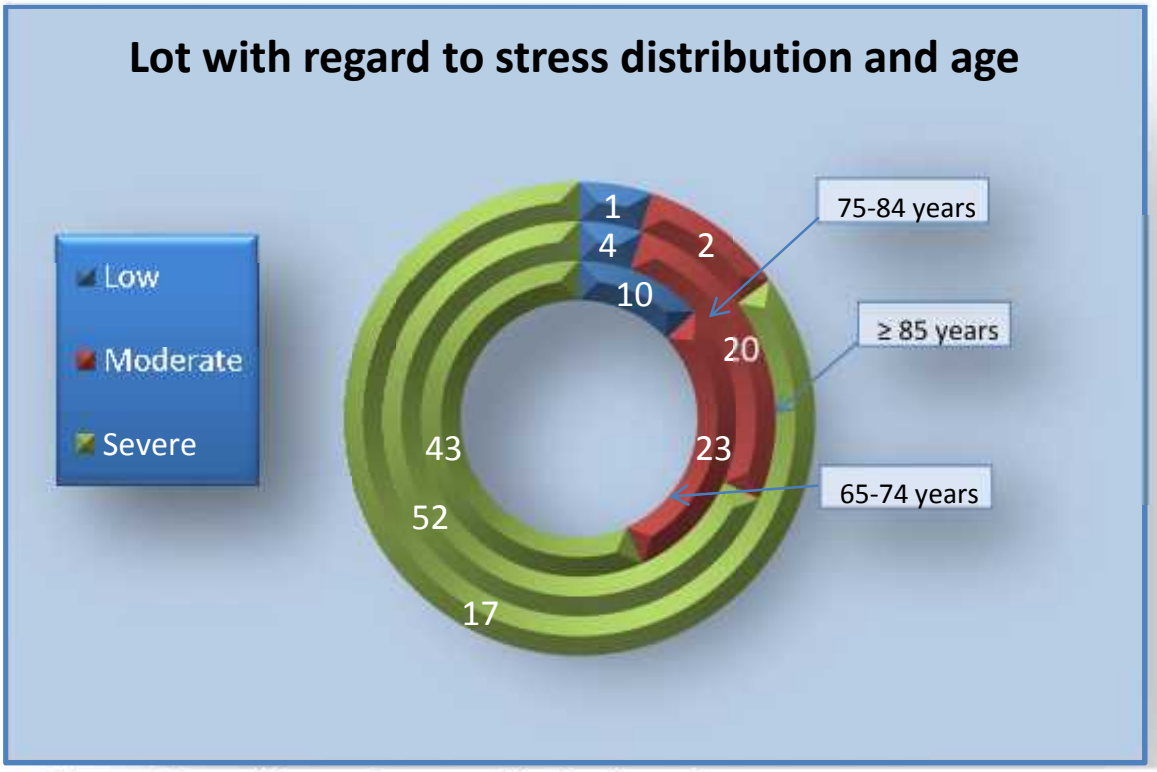


Figure 6. Lot with regard to stress distribution and age

Moderate and severe stress influenced the occurrence of pain in the study group, but only severe stress significantly correlated with the presence of upper gastrointestinal bleeding.

3.3. CLINICAL ASPECTS

All patients in the study group were symptomatic patients, without other symptoms of alarm, but symptoms intensity was large enough to require hospitalization and further investigations.

Morgner et al (2007) claimed that nearly 75% of patients on chronic NSAID users are not aware or concerned about possible gastric complications. [35] Asked about possible side effects, chronic users stated that they would be expected to alarm symptoms, before gastric complications, such as pain, dyspepsia. [36]

As uncomplicated symptoms, pain had the highest frequency (58.1%), followed relatively equal percentages of heartburn and nausea and vomiting (15%).

As complications, in the study group we encountered no cases of perforation or obstruction, but upper gastrointestinal hemorrhage only (manifested by haematemesis and / or melaena), present in 6.97% of cases. In all 12 patients was clinically significant.

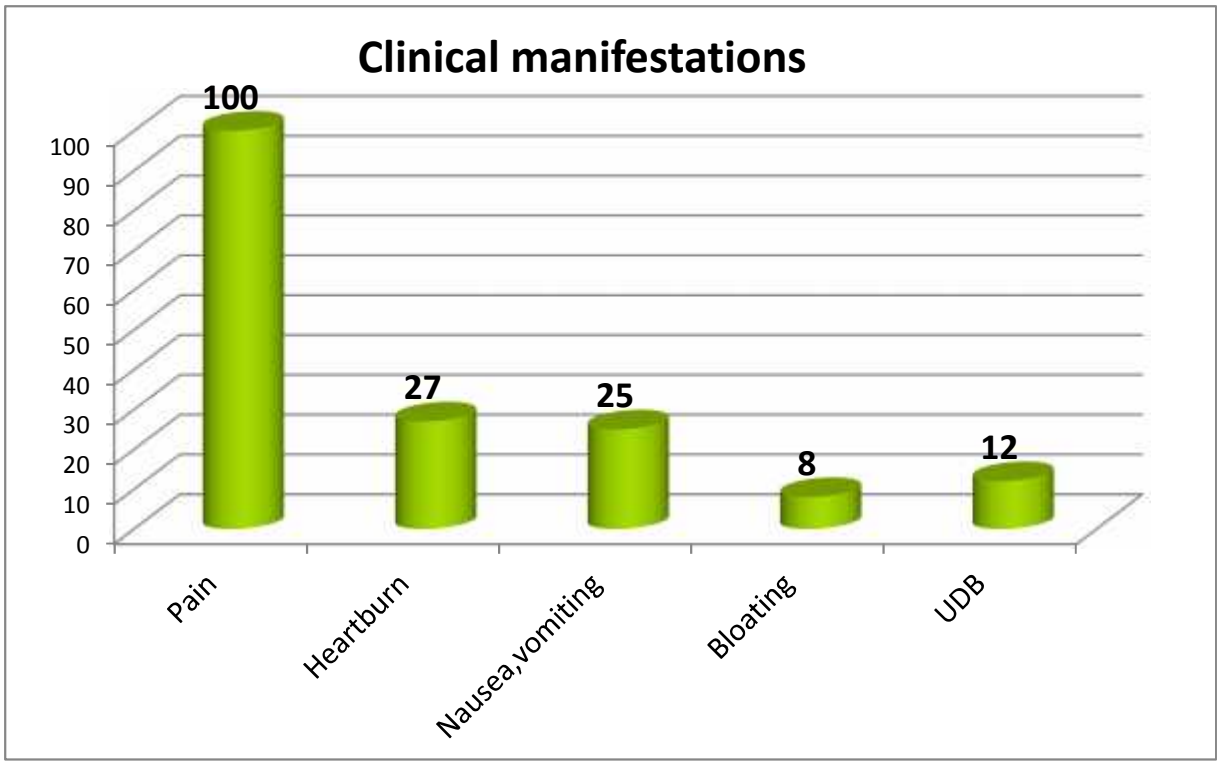


Figure 7. Clinical manifestations

Distribution of clinical manifestations by sex in the study group was as follows:
- Pain in 82 women (60.22%) and 18 men (50%)
- Heartburn in 20 women (14.7%) and 7 men (19.4%)
- UGB in 7 women (5.14%) and 5 men (13.88%)
- Bloating in 4 women (2.94%) and 4 men (11.1%)
- Nausea and vomiting in 23 women (16.91%) and 2 men (5.55%)

In Table 7 we presented the clinical manifestations depending on the sex and the whole lot.

Symptom	Males	Females	Total (%)	P
Pain	18(50%)	82(60,22%)	100 (58,13%)	0,266
Heartburn	7(19,4%)	20(14,7%)	27(15,69%)	0,487
Nausea and vomiting	2(5,55%)	23 (16,91%)	25(14,53%)	0,086
Bloating	4(11,1%)	4(2,94%)	8(4,65%)	0,038
UGB	5(13,88%)	7 (5,14%)	12(6,97%)	0,067

Analyzing the above data, we found a preponderance of pain both in women (60.22%) and men (50%). UGB frequency was higher in men than in women.

Analyzing statistical correlation, we observed that most of the symptoms does not correlate with sex, except bloating for which there was a statistically significant p ($p = 0.038$).

Next we analyzed the distribution of symptoms by age.

Distribution of symptoms by age showed that in group 65-74 years, pain was present in 50% of patients, followed by heartburn to a quarter of patients and there has been no case of UGB.

In the age group 75-84 years the pain was predominant symptom (64.47% of cases) followed by nausea and vomiting (15.78% of cases) and UGB (7.89% of cases).

With regard to upper GI bleeding is observed an exponential increase of its frequency from one age group to another, which is explained by accumulation of risk factors.

In the very elderly, over 85 years, pain dominated the clinical picture (65%), but we recorded a very high percentage of patients with UGB (30%).

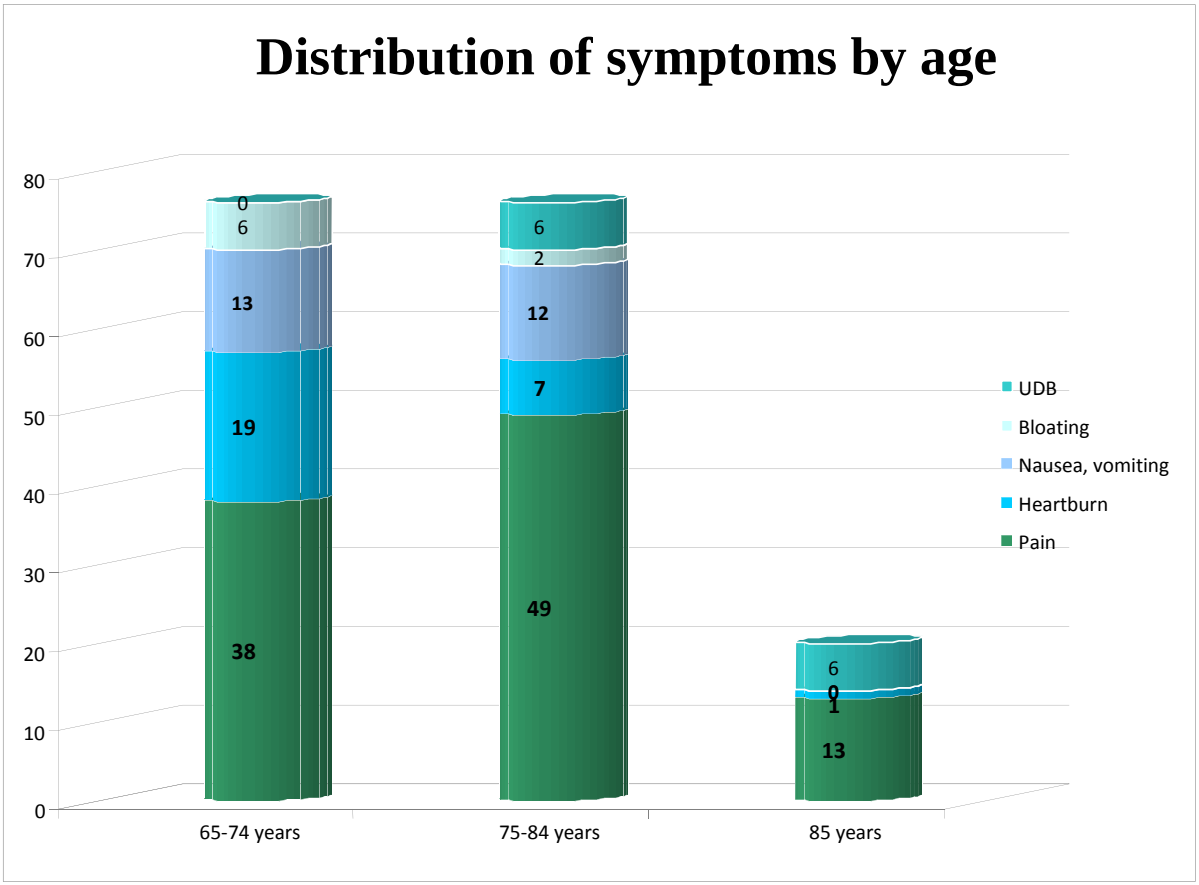


Figure 8. Distribution of symptoms by age

Correlations between symptoms and age

Although age is an independent risk factor for complications from literature data do not support the correlation between age and symptoms of uncomplicated (in some studies only a third of patients over 60 years experience painful symptoms). [37]

For this reason we wanted to watch if our group of study onset symptoms were correlated with patient age.

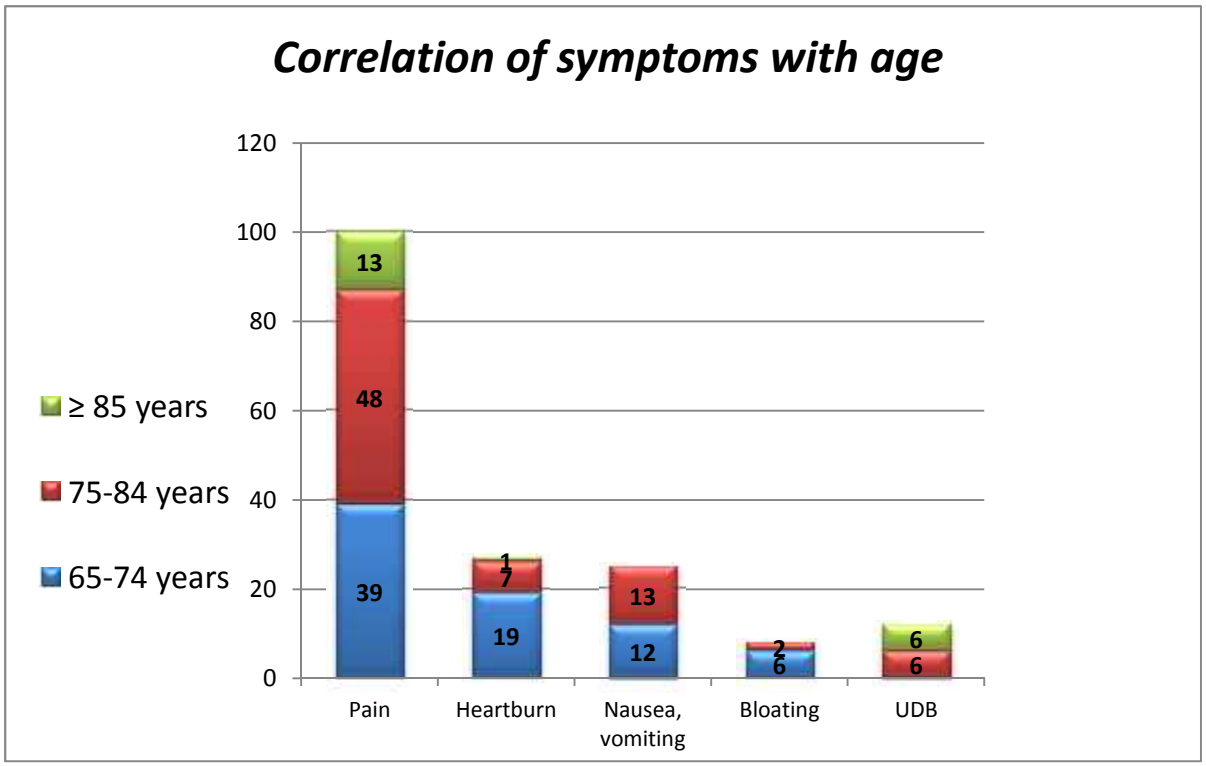


Figure 9. Correlation of symptoms with age

These correlations are presented in the table below.

Symptoms	**Age (p)**
Pain	0,587
Heartburn	0,031
Nausea and vomiting	0,611
Bloating	0,038
UGB	0,001

Table 8. Statistical correlation of symptoms with age

Surprisingly, although the pain was the most common symptom in all age groups regardless of sex, it did not correlate significantly with it. This could be explained by the fact that in elderly the perception of pain is unaltered, however the pain tolerance threshold is increased. [38]

However dyspeptic manifestations (heartburn, bloating) were correlated significantly with age p (0.031, 0.038 respectively). UGB also strongly correlated with age (p = 0.001), consistent to data in the literature. [39]

An important observation, analyzing the symptoms present on admission, is that the pain was very common, although not correlated neither with sex nor age (p = 0.587). UGB, both overall and by age group was most common (6.97%) in the study group compared to the literature (1-4%), with no correlation of it with sex [40] but only with age.

3.4. PARACLINIC EVALUATION

There isn't a battery of laboratory tests in the diagnosis of gastritis considered necessary, although in terms of possible complications (UGB) of comorbidities (diabetes, osteoarthritis, liver disease…) and the use of NSAIDs and oral anticoagulants for at least the usual tests must achieved.

Of laboratory tests collected from observation charts of patients, we considered useful to assess blood count, transaminases, inflammatory tests, blood glucose and creatinine in all patients, and evidence of coagulation in patients chronically treated with oral anticoagulants.

Anemia

Cell blood count (CBC) has been carefully investigated, in terms of the presence or absence of anemia secondary to upper gastrointestinal bleeding as a complication of NSAIDs gastritis. Classification of anemia based on hemoglobin level was as follows:

- easy: Hb ≥10 g% but less than 12-13g%
- average: Hb :7-10g%
- severe: Hb ≤7 g%.

In the study group anemia was present in three-quarters of patients (75.58%), being more frequent mild (95 patients) than average (35 patients).

Note that although the study group consisted of elderly patients with multiple comorbidities, we didn't record cases of severe anemia.

3.5. ENDOSCOPIC ASSESSMENT

Upper endoscopy is the "gold standard" in the diagnosis of gastritis, including those NSAIDs-induced and is considered safe and well tolerated even in the elderly [41]

Endoscopy is the exploration of choice, allowing direct visualization of specific lesions in the gastric mucosa. In addition, endoscopic examination allows highlighting other lesions (portal gastropathy, ulcers, tumors...).

The concept of "endoscopic gastritis" is accepted as recognition of its working group that formulated Sydney system for the classification of gastritis in 1990. [42]

While the types of injuries included in the classification of endoscopic gastritis are various (edema, erythema, flat or elevated erosion, exudate, vascular model, hyperplasia folds, folds atrophy, petechiae, nodularity), gastritis induced by NSAIDs have fewer endoscopic changes. Lesions may be: erythematous, erosive (erosions even bleeding) and / or ulcerations.

In the vast majority of patients, gastric mucosal lesions are superficial and self-limiting. The spectrum of endoscopic lesions caused by NSAIDs includes a combination of subepithelial hemorrhages with erosions and ulcers, which usually referred to as the NSAIDs gastropathy. The distinction between erosions and ulcers depends on histopathological definition, erosion is defined as complying mucosa lesions and ulcers that penetrate to submucosal lesions.

For practical reasons, endoscopic definition is used, based on a subjective assessment of the size, shape and depth of lesions. Endoscopic described, erosions are somewhat smaller and more superficial, while ulcers tend to be larger (more than 5 mm in diameter) and deeper. [43]

In our study group patients had endoscopic lesions following:

• erythema: 51.17%

• erosions: 16.28%

• ulcerations (single / multiple): 32.54%

Endoscopic aspect	Patients (no)	Percentage
Erythema	88	51,17%
Erosions	28	16,28%
Ulcerations (single/multiple)	56	32,54%

Table 9. Endoscopic aspects encountered in the study group patients

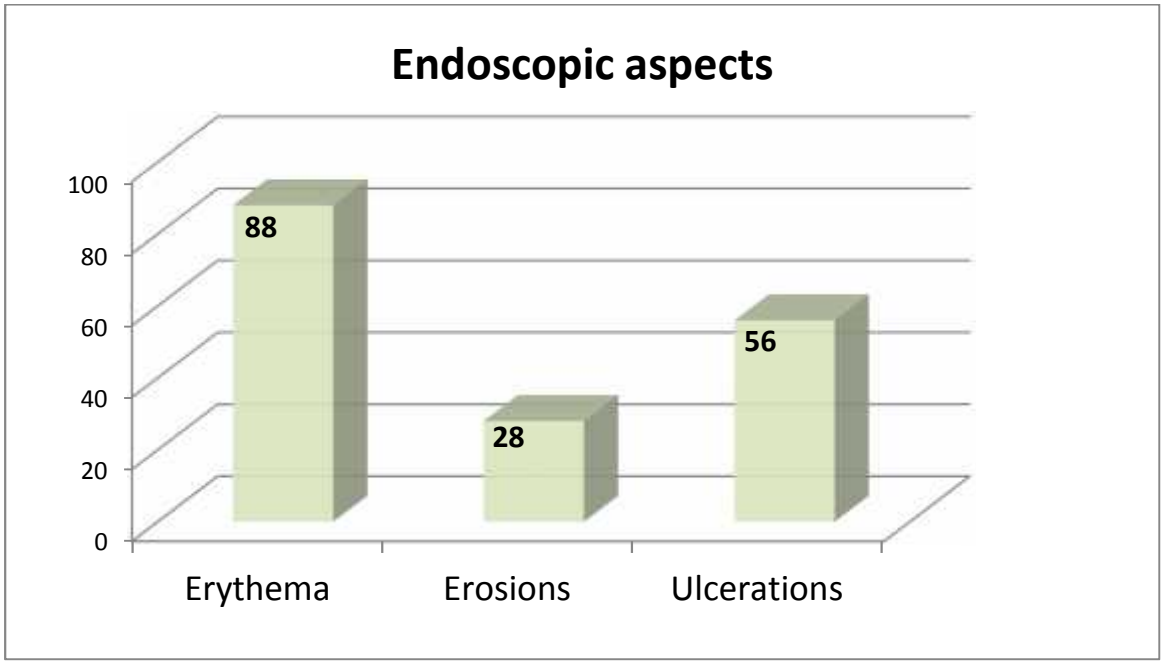


Figure 10. Distribution of endoscopic lesions in the study group

Please note that erosions described endoscopic had no recent bleeding stigmata in any patient, while ulcerations had no stigmata of bleeding in 42 patients and presentied signs of bleeding in 14 patients.

These basic endoscopic gastric mucosal lesions were combined in different basic types of NSAIDs gastritis. Such forms of gastritis after endoscopic NSAIDs were:

- Exudative -erythematous gastritis: is the area of erythema of 2-3 mm that are disseminated in mucosa of normal appearance and can be covered by a whitish exudate. This type of gastritis was present in 88 patients (51.16%)

- Maculo-erosive gastritis: appears as focal erythematous patches 3-15 mm in diameter, there are superficial ulcers covered with fibrino- leukocyte debris, gray and white. When these ulcers are large, surrounding erythema appears as a red glow at the edge of ulceration. Maculo-erosive gastritis was characterized by erosions in 28 patients or non-bleeding ulcers in 42 patients (24.41%).

- Haemorrhagic gastritis: lesions that appear are the type of single or multiple ulcers that may look different depending on the time of endoscopy (from the onset or cessation of

bleeding). During the active period, bleeding appeared as bleeding points, bleeding spots circumscribed or diffuse. During posthaemorrhagic recent period (within 6 hours after cessation of bleeding), puncture wounds, cracks or areas of 3-5 mm covered by blood clots occur.

According to this classification distribution of patients in the study group was that shown in the table below:

Endoscopic gastritis	**Endoscopic lesions**			
	Erythema	**Erosions**	**Ulcerations**	**Total (%)**
Erythematous gastritis	88	0	0	88(51,17%)
Erosive gastritis	0	28	42	70 (40,69%)
Haemorrhagic gastritis	0	0	14	14 (8,14%)

Table 10. Endoscopic gastritis distribution in the study group

Next we presented the distribution of endoscopic lesions encountered in the study group according to sex.

Gender	**Endoscopic lesions**		
	Erythema	**Erosions**	**Ulceraions (single/multiple)**
Males	20 (55,55%)	5 (13,88)	11 (30,55%)
Females	68 (50%)	23 (16,91%)	45 (33,08%)
Total	88	28	56
Percentage	51,17%	16,28%	32,54%

Table 11. Endoscopic lesions by gender

The most common type of endoscopic lesion was erythema, both in men and women, and the whole group, with a rate of over 50%. Single or multiple ulcerations were found in approximately one third of patients in the study group (32.54%), both in men and women. Erosions had the lowest frequency in both sexes and in the entire group (16.28%).

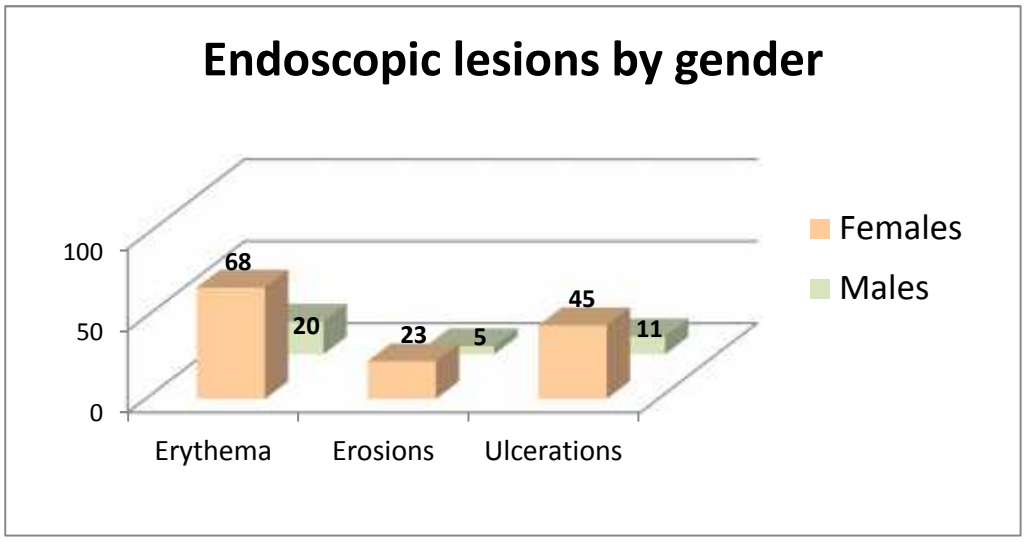


Figure 11. Endoscopic lesions by gender

Given the importance of age in post NSAIDs gastritis appearance, we considered important to study the distribution of endoscopic lesions by age.

Age groups	**Endoscopic lesions**		
	Erythema	**Erosions**	**Ulcerations (single/multiple)**
65-74 years	47 (61,84%)	1 (1,31%)	28 (36,84%)
75-84 years	36 (47,36%)	18 (23,68%)	22 (28,94%)
≥85 years	5 (25%)	9 (45%)	6 (30%)

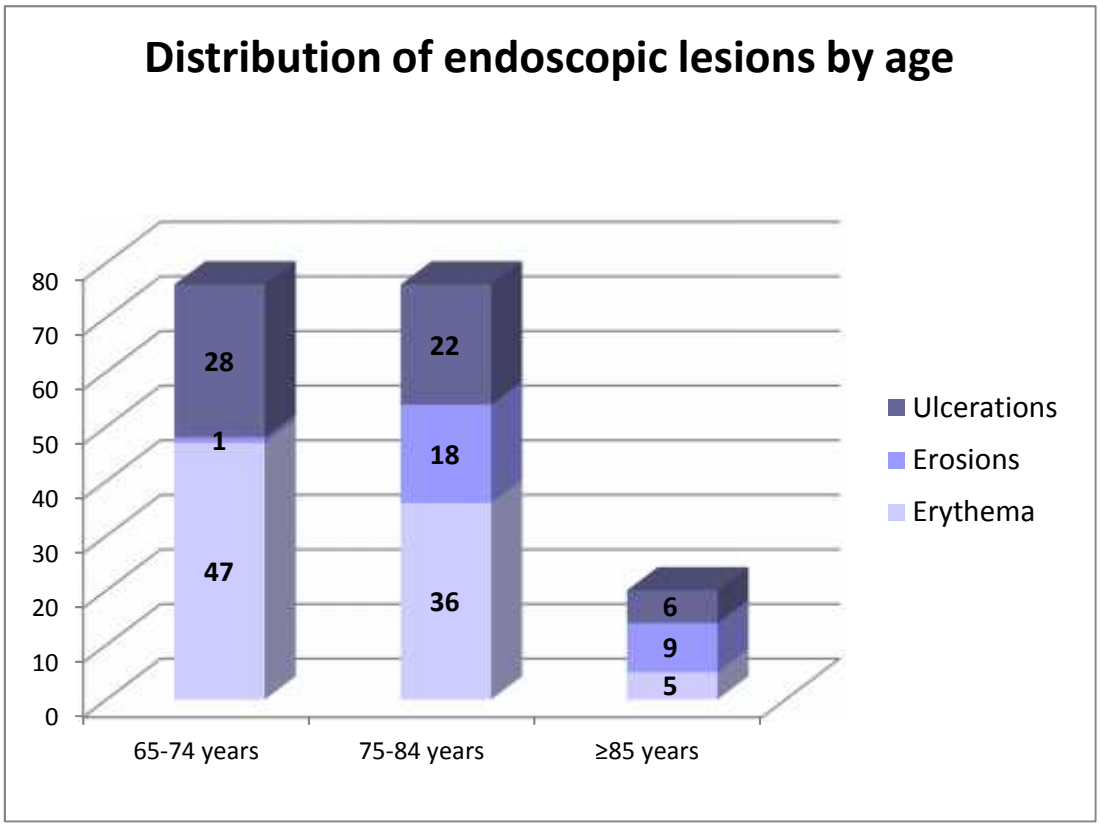
Table 12. Distribution of endoscopic lesions by age

In the age group 65-74 years erythema was seen in 47 patients (61.84%), ulceration in 28 patients (36.84%) and erosions were present in one patient (1.31%).

In patients aged 75-84 years erythema was present in almost half of them (47.36%), followed by relatively equal frequency of ulcers and erosions.

Very elderly patients over 85 years the most common injuries were erosions (45%), followed in relatively equal proportions of erythema and ulceration (25%).

In conclusion, we can say that, in terms of endoscopic appearance, erythema was seen in half of Lot patients (51.17%) but in terms of distribution by age, progressively decreases as frequency, erosion had the lowest frequency (16.28%), maintaining constant frequency as age, whereas ulcers were present in 32.54% of patients, with an exponential increase in frequency with age.



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Correlations between symptoms and endoscopic aspects

After accepting the concept of "endoscopic gastritis" the working group formulated Sydney system for the classification of gastritis in 1990 [42], it was questioned whether there is a correlation between clinical symptoms, endoscopic and histological diagnosis of chronic gastritis post NSAIDs.

Such a study conducted on 50 patients consuming NSAIDs has been shown that there is a weak correlation of symptoms with endoscopic appearance. [44]

The same results have emerged in another study of prevalence pursued post-NSAID gastritis. [45]

Next we aimed to correlate symptoms with endoscopic aspects of our group patients.

Simptoms/Endoscopic aspects	Erythema	Erosions	Ulcerations
Pains	0,719 (50)	0,048 (21)	0,241 (29)
Heartburn	0,182(17)	0,428(3)	0,423(7)
Nausea and vomiting	0,601 (14)	0,967(4)	0,599(7)
Bloating	0,167 (6)	- (0)	0,640(2)
UGB	0,002(1)	- (0)	0,001(11)

Table 13. Correlation of symptoms with endoscopic lesions

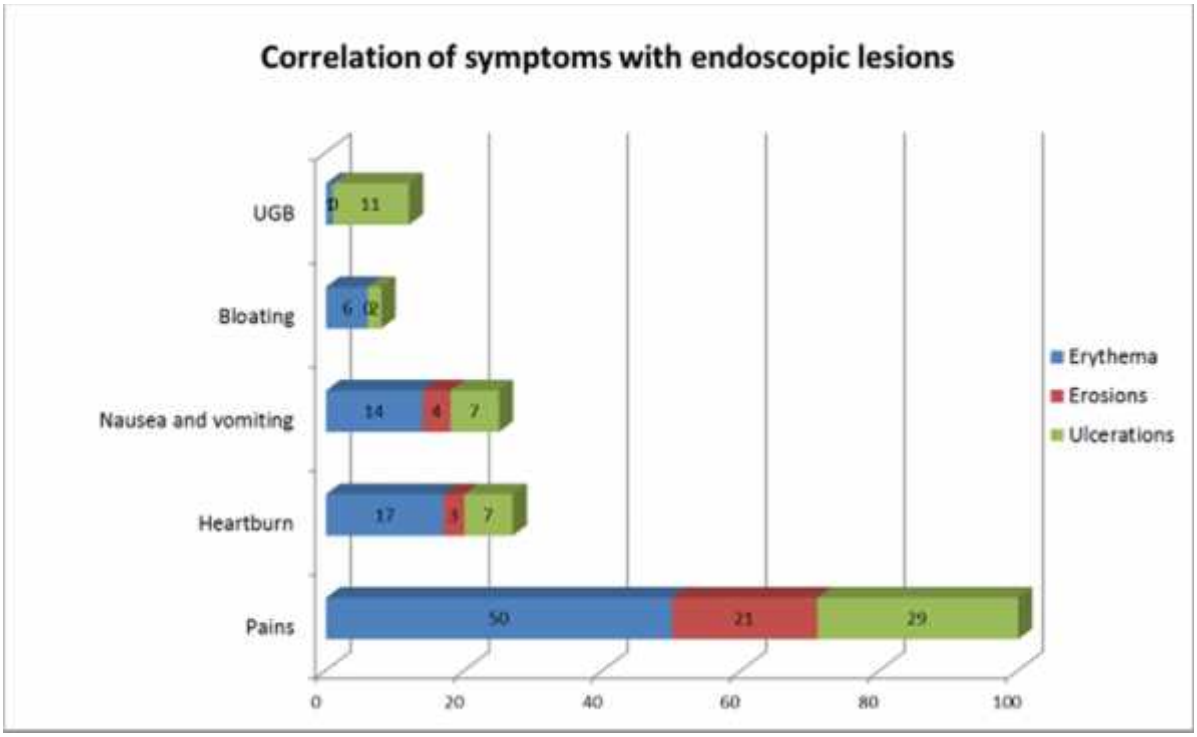

Figure 16. Distribution lot depending on the symptoms and appearance of EDS

In terms endoscopic, of the 100 patients with pain 50 had erythema, 21 gastric erosions and 29 patients single or multiple ulcers.

Although half of the patients with pain had endoscopic appearance of erythema of gastric mucosa (50 of 100, 50%), pain was not significantly correlated only with erosions ($p = 0.048$).

27 patients with heartburn had endoscopic appearance of erythema (17), erosions (3), ulceration (7) and there is no correlation between these symptoms and endoscopic lesions.

The same can be said about the 25 patients with nausea and vomiting (14 with erythema, erosions and 7 4 with ulceration).

Neither the 8 patients who had symptom onset bloating as there was no correlation with endoscopic description of gastric lesions (6 of erythema, 2 and no patients with erosions, ulcers).

In the patients with complicated clinical symptoms (UGB), one patient experienced erythema, while 11 patients had ulcers. UGB was significantly correlated with both erythema ($p = 0.002$) and ulceration ($p = 0.001$).

3.6. HISTOPATHOLOGICAL EVALUATION

Histopathological examination is not a routine evaluation for post NSAIDs gastritis, which is why in our group study was conducted in 100 of the 172 patients, including 22 men and 78 women.

Patients with biopsy distribution by age was as follows:

¬ 65-74 years: 42 of 76 (55.26%)

¬ 75-84 years: 44 of 76 (57.89%)

¬ ≥85 years: 14 of 20 (70%)

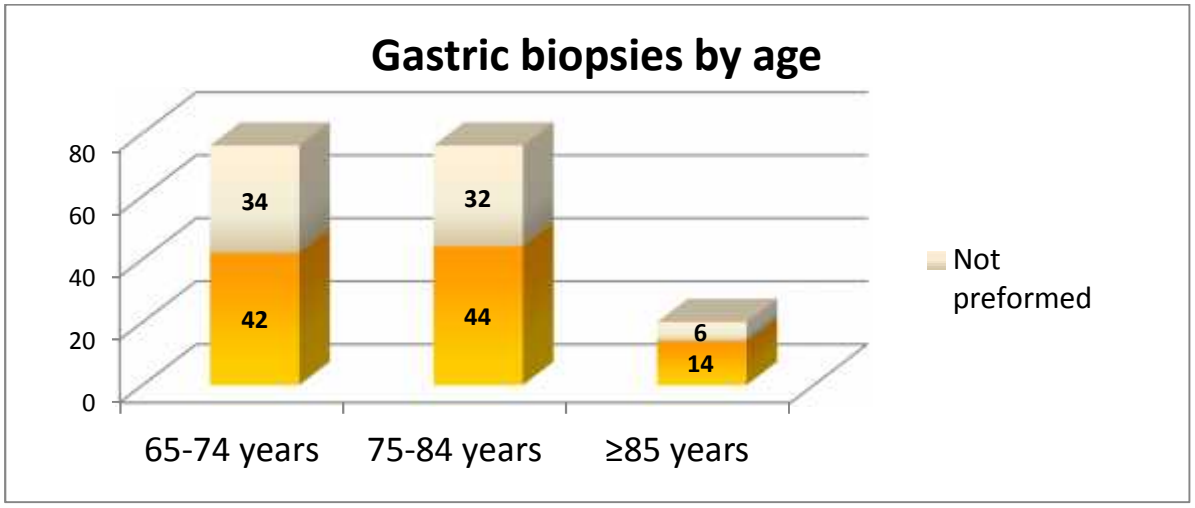

Figure 17. Gastric biopsies by age

Greater percentage of biopsy in the very elderly could be explained by a desire to exclude the possibility of malignancy by all means.

Some investigators suggest that gastric biopsy should not be performed routinely during gastroscopy, but this view was authoritarian rejected by Carpenter and Talley, who pointed out that biopsy should be an integral part of endoscopic examination, because even a single experienced gastroenterologist is not enough, but only histological examination ensures accurate diagnosis of gastritis. The Sydney is the most widely use system for standardized reporting of gastric biopsies. [47]

Types of injuries described in the subgroup of study histopathology were erosions, foveolar hyperplasia and edema, hemorrhagic lesions, malignant lesions or combinations.

Note that in all 100 patients, histopathology described a minimal to moderate inflammatory infiltrate (limfoplasmocitic type), suggesting a chronic inflammation of the gastric mucosa. On the other hand, as stated above, the presence of inflammation strongly supports diagnosis of gastritis after NSAIDs.

Next we discussed distribution of histopathological lesions in patients according to gender and age groups.

Regarding gender distribution, in men prevailed erosions (40.9%) and hyperplasia and edema, as hemorrhagic lesions (22.72%). Malignancy was present in 4.54% of men.

In women, erosions predominated (44.87%), followed by hyperplasia and edema associated to erosion (23.07%) and solitary (19.23%), indicating that hemorrhagic lesions

were twice uncommon as frequency than in males (11.53%), and malignancy with very low frequency (1.28%).

On the whole study group, the dominant histopathological lesions were erosions (44%), both in men and women, followed by hyperplasia and edema and their association in equal proportions (20%). Hemorrhagic lesions occurred with a frequency of 14% is twice as common in men, and malignancy (2%) was more common in men than in women.

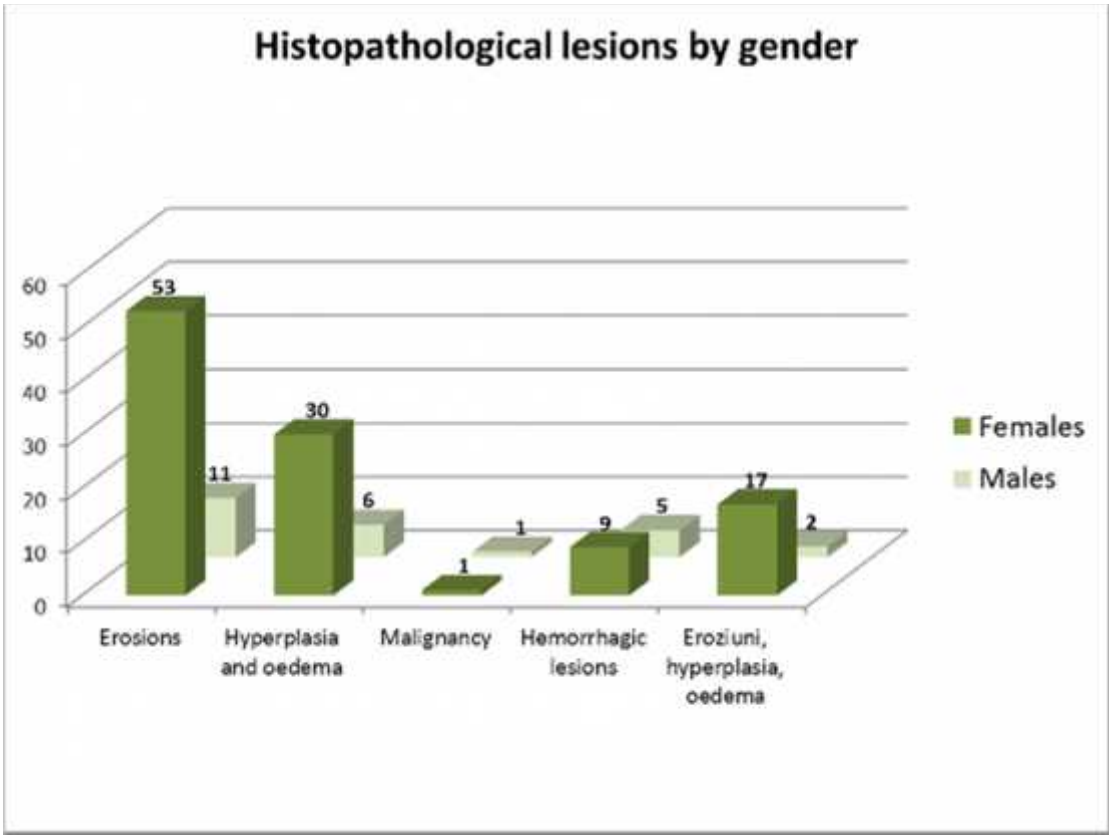

Figure 18. Histopathological lesions by gender

Age distribution of histopathological lesions was analyzed further.

Erosions were the most common, and malignancy was absent in age groups 65-74 and 75-84 years. Age group 65-74 years were absent and hemorrhagic lesions, but patients between 75-84 years showed such lesions at a rate of 13.63%.

Most severe lesions (malignancy, hemorrhagic lesions) were predominant in the very elderly, over 85 years (the 2 cases of malignancy and 8 of the 14 cases with hemorrhagic lesions -57.14% as the frequency of lesions in this group age).

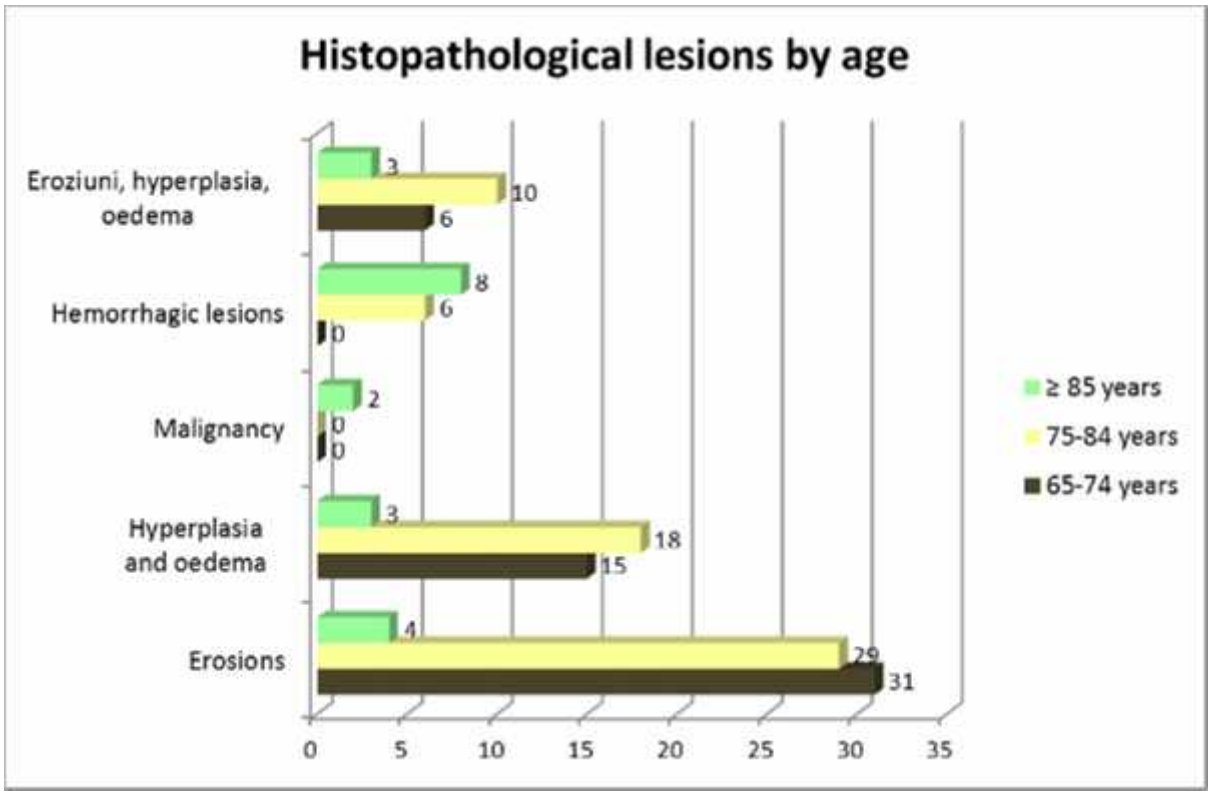

Figure 19. Histopathological lesions by age

Because dyspeptic symptoms are not a very specific warning, it is very important to identify factors that increase the risk of severe gastrointestinal complications and to determine ways to reduce this risk.

The correlation between symptoms and histopathological examination

Numerous studies show however that we can not establish a correlation between symptoms and histopathology, nor between endoscopic and histological appearance. [44]

For example many ulcerations of the antrum and prepiloric area are typical for NSAIDs –induced gastritis, but sometimes it is hard to differentiate them from HP ulcerations or gastric cancer. [46]

For this reason we wanted to see if our group could establish a correlation between symptoms and histological descriptions.

Thus, of the 100 patients admitted for pain, 52 had gastric biopsy and histopathology. At these patients, histopathological lesions described were: erosions (25 patients), hyperplasia and edema (12 patients), hyperplasia and edema associated with erosions (11 patients) and hemorrhagic lesions (4 patients).

Of the 18 patients with heartburn who performed biopsy, 11 had epithelial erosions, 3 hyperplasia and edema, and 4 had erosion associated with these . The 14 patients with nausea and vomiting experienced erosion (5), hyperplasia and edema (4), hyperplasia, edema and erosions (5). Patients with bloating experienced erosion (3), hyperplasia and edema (1).

Upper gastrointestinal bleeding is a major complication of NSAIDs gastritis, so that all 12 patients with UGB performed gastric biopsy during endoscopy and histopathology.

Symptoms/ Histopathologic aspects	Erosions	Hyperplasia and edema	Hemorrhagic lesions	Malignancy	Erosions, hyperplasia and edema
Pain	0,248(25)	0,119(12)	0,042(4)	- (0)	0,352(11)
Heartburn	0,033(11)	0,469(3)	-(0)	-(0)	0,824(4)
Nausea and vomiting	0,481(5)	0,104(4)	-(0)	-(0)	0,200(5)
Bloating	0,697(3)	0,609(1)	-(0)	-(0)	-(0)
UGB	-(0)	-(0)	0,000(10)	0,000(2)	-(0)

Table 14. The correlation between symptoms and histopathological lesions

Of the 18 patients with heartburn who performed biopsy, 11 had epithelial erosions, 3 hyperplasia and edema, and 4 had erosion associated with these . The 14 patients with nausea and vomiting experienced erosion (5), hyperplasia and edema (4), hyperplasia, edema and erosions (5). Patients with bloating experienced erosion (3), hyperplasia and edema (1).

Upper gastrointestinal bleeding is a major complication of NSAIDs gastritis, so that all 12 patients with UGB performed gastric biopsy during endoscopy and histopathology.

Histopathological description in patients with UGB corresponded to hemorrhagic lesions (10 patients), correlated with high p statistically significant ($p < 0.001$). We note that in 2 patients UGB was accompanied by the presence of malignant lesions and correlated with them ($p < 0.001$)

An important observation is that the two patients who had malignant lesions on histopathology had no endoscopic changes to attract attention to a possible malignancy. This could support the idea that for elderly patients, especially if there are alarm symptoms, it is necessary to undergo gastric biopsies.

The correlation between endoscopic aspect and histopathological examination

Results from many studies, regarding the correlation between endoscopic appearance and histological description, are contradictory, however, given the increased incidence of malignancy in the elderly population, histological examination has become a necessity. [44, 46]

For this reason we wanted to analyze this issue in the study group patients.

Endoscopic aspect / Histophatologic examination	Epithelial erosions	Hyperplasia and edema	Malignancy	Hemorrhagic lesions	Erosions + hyperplasia + edema
Erythema	0,110 (22)	0,156 (20)	- (0)	0,013 (2)	0,004 (3)
Endoscopic erosions	- (0)	0,020 (9)	- (0)	0,274 (3)	0,000 (9)
Ulcerations	0,243 (22)	0,003 (8)	0,095 (2)	0,077(9)	0,987 (8)

Table 15. Correlation of endoscopic lesions with histopathological examination

53.40% of patients with erythema (47 of 88), 42.85% of patients with endoscopic erosions (12 of 28) and 73.21% of those with ulcers (41 of 56) performed gastric biopsies, followed by histopathologic examination.

Analyzing the above percentages noted that most patients with ulceration performed biopsies, this probably due to the fact that ulcers are most severe endoscopic lesions.

Half of patients with epithelial erosions had endoscopic appearance of erythema, and half of ulceration.

Patients with hyperplasia and edema predominantly showed endoscopic appearance of erythema, but also endoscopic erosions ($p = 0.020$) and ulceration, which both correlated ($p = 0.003$). Patients with malignant lesions had only endoscopic appearance of the ulcer, without a statistically significant correlation ($p = 0.095$).

Association of epithelial erosion with hyperplasia and edema (to histopathology) was present in 15% of patients with erythema (3 of 20), 45% with endoscopic erosions (9 of 20) and 40% of those with ulcers (8 20), correlated significantly with erythema ($p = 0.004$) and endoscopic erosions ($p = 0.000$).

14.28% of patients with hemorrhagic lesions (2 of 14) had endoscopic appearance of erythema with statistic significance (p=013), 21.42% (3 of 14) endoscopic appearance of erosions, and 64.29% (9 of 14) endoscopic appearance of ulcers.

3.7. RISK FACTORS FOR COMPLICATIONS OF NSAIDs GASTRITIS

Many studies have been designed to identify patients with the highest risk of developing side effects with NSAIDs.

Certain risk factors
Age >65 years
Ulcer history
High doses or associations of NSAIDs
Concomitant use of ASA or oral anticoagulants
Concomitant use of corticosteroids
Severe systemic diseases (comorbidities)
Possible risk factors
Concomitant HP infection
Smoking
Alcohol consumption

Table 16. Risk factors for gastric complications from NSAIDs

Age is an independent risk factor for gastritis, very important fact in the study group, as all the patients are over 65.

Other risk factors identified in multiple studies are: high doses of NSAIDs (including concurrent use of two or more NSAIDs), history of ulcers or gastrointestinal bleeding, concomitant use of corticosteroids or so, major comorbidities and concomitant use of anticoagulants. [48]

Possible risk factors include HP infection, alcohol consumption and smoking. Since the last two risk factors were analyzed in the chapter on behavior and lifestyle, we further analyze other risk factors.

A. Infection HP

Identification of HP infection as a risk factor for the development of gastritis and ulcers raised the question of a possible synergistic relationship between the presence of HP infection and NSAID use.

Although two prospective studies have suggested a synergistic relationship, showing that HP infection significantly decreases ulcer rates in users of NSAIDs (Bianchi Porro et al., 1996 and Chan et al. 1997) [49, 50], numerous studies have found these two as independent factors. [51, 52, 53]

Infection with Helicobacter pylori is a Gram-negative chronic gastric infection, whose incidence increases with age everywhere.

HP infection was determined in a subset of 121 patients (70.34%) using a rapid urease test on gastric biopsy specimens obtained. Rapid urease test has been validated as a test to diagnose HP infection, with very good sensitivity and specificity, even in elderly patients.

HP infection	Patients	Percentage
Not tested	51	29,65%
Positive	68	39,53%
Negative	53	30,81%

Table 17. Testing of Helicobacter pylori infection in the study group

Distribution of HP infection in the study group correlated with age groups is presented below. Of the 121 patients who underwent testing, 68 were HP positive (57.02%) and the remaining 53 were HP negative (42.96%), in agreement with literature data showing a prevalence of infection HP above 50% in the elderly. [54, 55]

However for patients with chronic use of NSAIDs, literature data showed a lower prevalence of HP infection. Thus was launched the hypothesis that gastric environment created by the use of NSAIDs could be unfavorable for implantation HP, terms confirmed that NSAIDs have a germicidal effect. On the other hand, HP protects consumers chronic NSAID gastric complications develop by stimulating mucosal PG synthesis. [56]

HP infection distribution by gender is presented in the table below.

HP infection	Males	Females
Not tested	13	38
Positive	19	49
Negative	4	49

Table 18. HP infection by gender

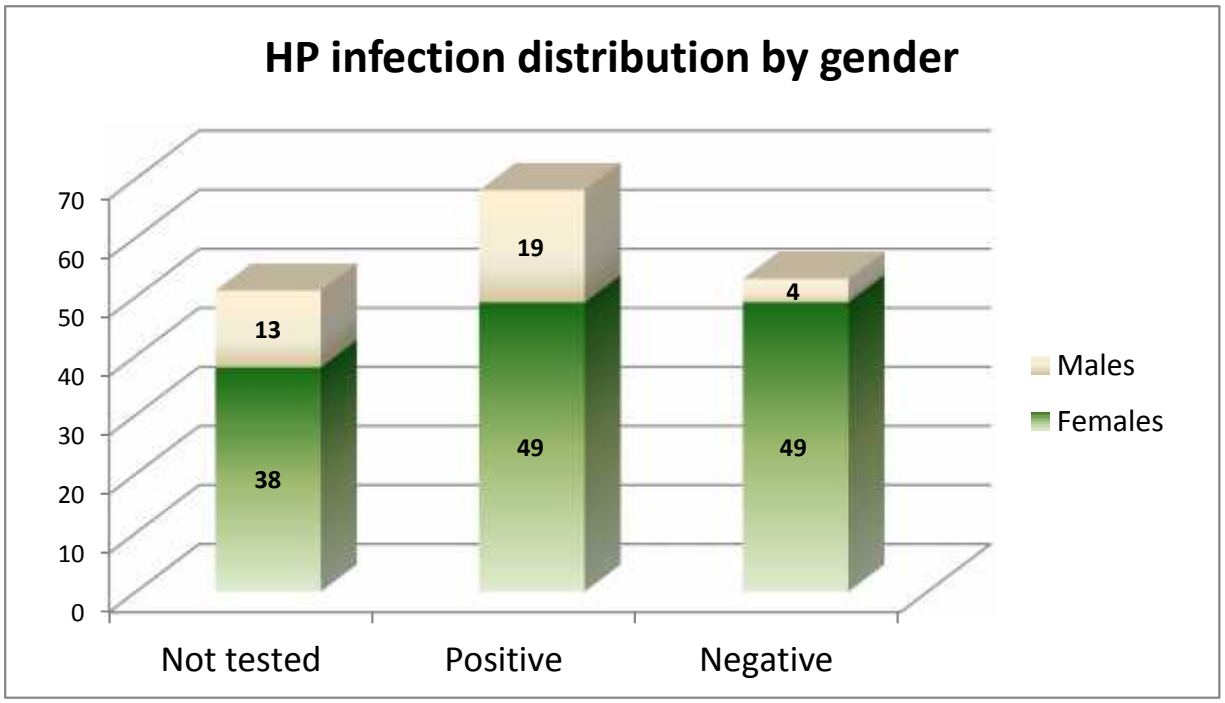

Figure 20. HP infection distribution by gender

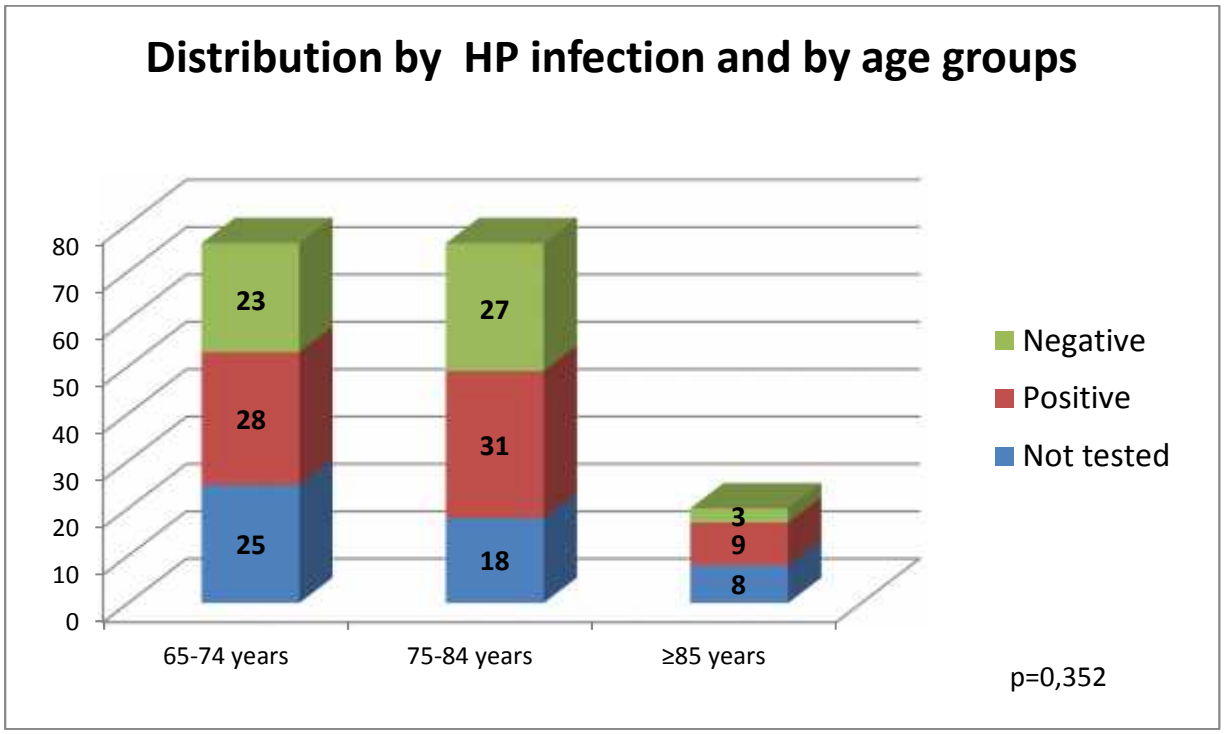

Figure 21. Distribution by HP infection and by age groups

In view of the importance transmission mode (and hence living and socioeconomic conditions) the prevalence of HP infection, we considered useful correlation between HP infection source environment. Thus patients who are tested HP, 90 were from urban areas and 31 in rural areas. In urban areas the infection rate was 53.33% (48 of 90 patients) and 64.51% in rural areas (20 of 31 patients), which may correlate with the sanitary conditions

theoretically lower in rural areas. But the correlation was not statistically significant p (p = 0.179).

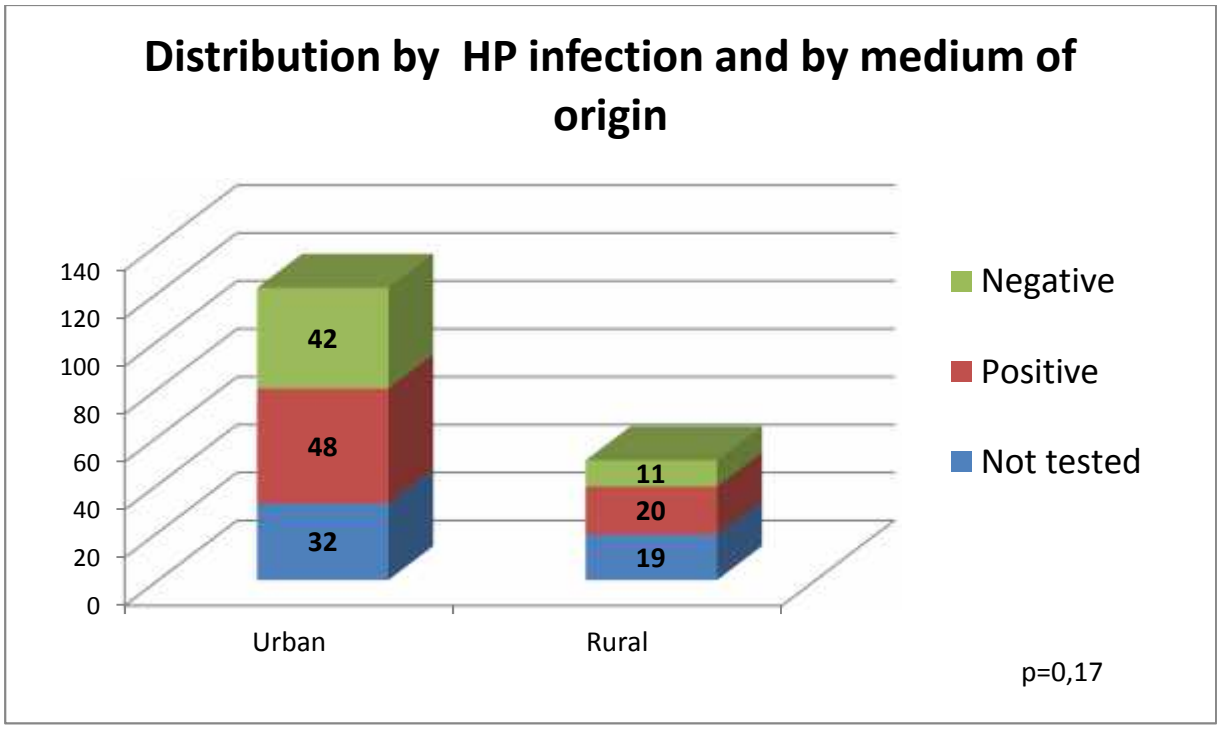

Figura 22. Distribution by HP infection and by medium of origin

Correlation between HP infection and symptoms

As mentioned above, HP infection and chronic use of NSAIDs are two independent risk factors for gastritis and their complications.

For this reason we divided the 121 patients who made rapid urease test for HP infection in two subgroups, namely HP positive (68 patients) and HP negative (53 patients).

For the two subgroups, we analyzed the distribution of initial symptoms, trying to see if there is a correlation with HP infection.

The data obtained are presented in the table below.

Symptoms	HP positive	HP negative	p
Pain	32	38	0,007
Heartburn	11	6	0,448
Nausea and vomiting	12	6	0,334
Bloating	4	1	0,275
UGB	9	2	0,074

Table 19. Correlation between HP infection and symptoms

Of all the symptoms, in our study group, pain alone was statistically significantly correlated with HP infection (p = 0.007). Thus, we might consider useful for patients with severe stomach pain, refractory to conservative treatment, to perform RUT.

Correlation of HP infection with endoscopic lesions

Endoscopic aspects	HP positive	HP negative	p
Erythema	28	27	0,286
Endoscopic erosions	12	9	0,924
Ulcerations single/multiple	28	17	0,306

Table 20. HP infection correlation with endoscopic lesions

Reviewing the literature we found no data showing a link between HP infection and endoscopic changes and often it is difficult to differentiate the damage caused by NSAIDs from that due to HP infection.

Neither in the study group we found no correlation between endoscopic lesions and HP infection.

Correlation of HP infection with histopathological aspects

Histopathologic aspects	HP positive	HP negative	p
Erosions	27	18	0,510
Hyperplasia and oedema	16	12	0,422
Hemorrhagic lesions	10	2	0,109
Malignancy	2	0	-
Erosions, hyperplasia and oedema	11	6	0,857

Table 21. Correlation of histopathological lesions with HP infection

Histopathological changes caused by HP infection are difficult to distinguish from those due to chronic use of NSAIDs. For this reason histopathological lesions described in patients in our study could not correlate with HP infection.

B. Consumption of NSAIDs in high doses or combinations

Monitoring medication they take geriatric patients is crucial to their health and well-being. Many of them consume daily NSAIDs as self-medication (OTC) for different complaints. Even taken properly, these drugs can cause in elderly many gastric and cardiovascular side effects. Because of comorbidities common in the elderly, such as osteoarthritis or degenerative joint disease, NSAIDs are necessary and indeed reduce pain.

All patients in the study group were considered chronic users of NSAIDs criterion defined as the consumption of NSAIDs at least 14 days past 3 months at any dose.

NSAIDs used by patients were divided into two categories:

• Group I (conventional) non-selective NSAIDs or indomethacin, diclofenac, ketoprofen, piroxicam;

• Group II (new) selective NSAIDs and specific, that meloxicam, celecoxib, etoricoxib.

124 patients (72.09%) have used non-selective NSAIDs, while 48 patients (27.90%) had used NSAIDs selective and specific.

Between patients consume NSAIDs group we've seen 108 patients who consumed one NSAID (81 patients in the therapeutic dose and high-dose 17 patients), 16 patients who

consumed two NSAID-associated (14 patients in therapeutic doses and 2 patients in doses large).

Note that all the other 48 patients had consumed a single selective NSAIDs or specific therapeutic dose only.

NSAIDs group I (124 patients)		**NSAIDs group II (48 patients)**
• **A single NSAIDs group I**		Meloxicam**:**9F+1M=10
Therapeutic dose 81	Indometacin: 7F+1M=8	Celecoxib:13F+7M=20
	Diclofenac: 25F+5M=30	Etoricoxib: 16F+2M=18
	Ketoprofen: 26F+8M=34	
	Piroxicam: 8F+1M=9	
High dose 27	Diclofenac:9F+3M=12	
	Ketoprofen: 10F+2M=12	
	Piroxicam: 3F	
• **Association of two NSAIDs group I**		
Therapeutic dose 14	Diclofenac+Indometacin:4F+1M=5	
	Diclofenac+Ketoprofen:3F+3M=6	
	Diclofenac+Piroxicam:1F+2M=3	
High dose 2	Diclofenac+Piroxicam: 2F	

Table 22. Distribution of patients by type of NSAID used (F-women, M-men)

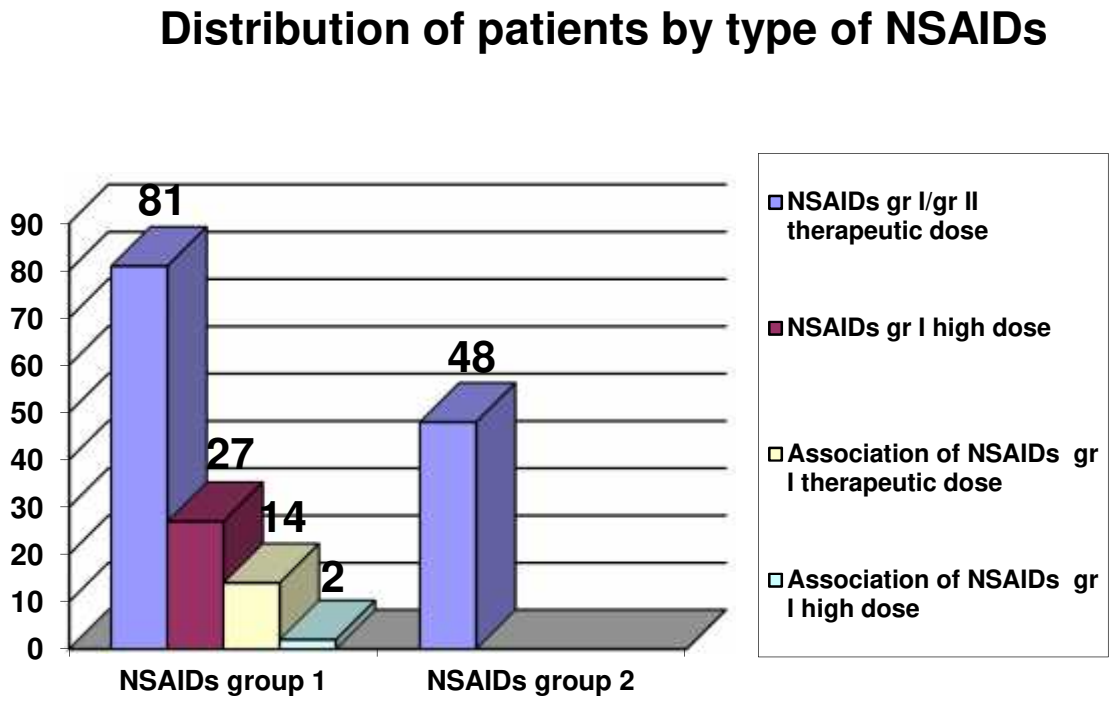

Figure 23. Distribution of patients by type of NSAIDs

Patient distribution by type of NSAID consumed and sex is shown in table and graph below.

NSAIDs of group II were preferred by 38 women and 10 men in identical proportion (27%).

NSAIDs/Gender	Females	Males	p
NSAIDs group I	98	26	0,985
NSAIDs group II	38	10	0,985

Table 23. Patient distribution by type of NSAID and gender

From the above data on the study group observed that 98 women and 26 men had used NSAIDs group I and also that 32 women out of 136 (23.52%) used high doses or association of NSAIDs group I versus 11 men in 36 (30.55%). Greater percentage of high-dose or combination of men could be explained by their lower tolerance to pain.

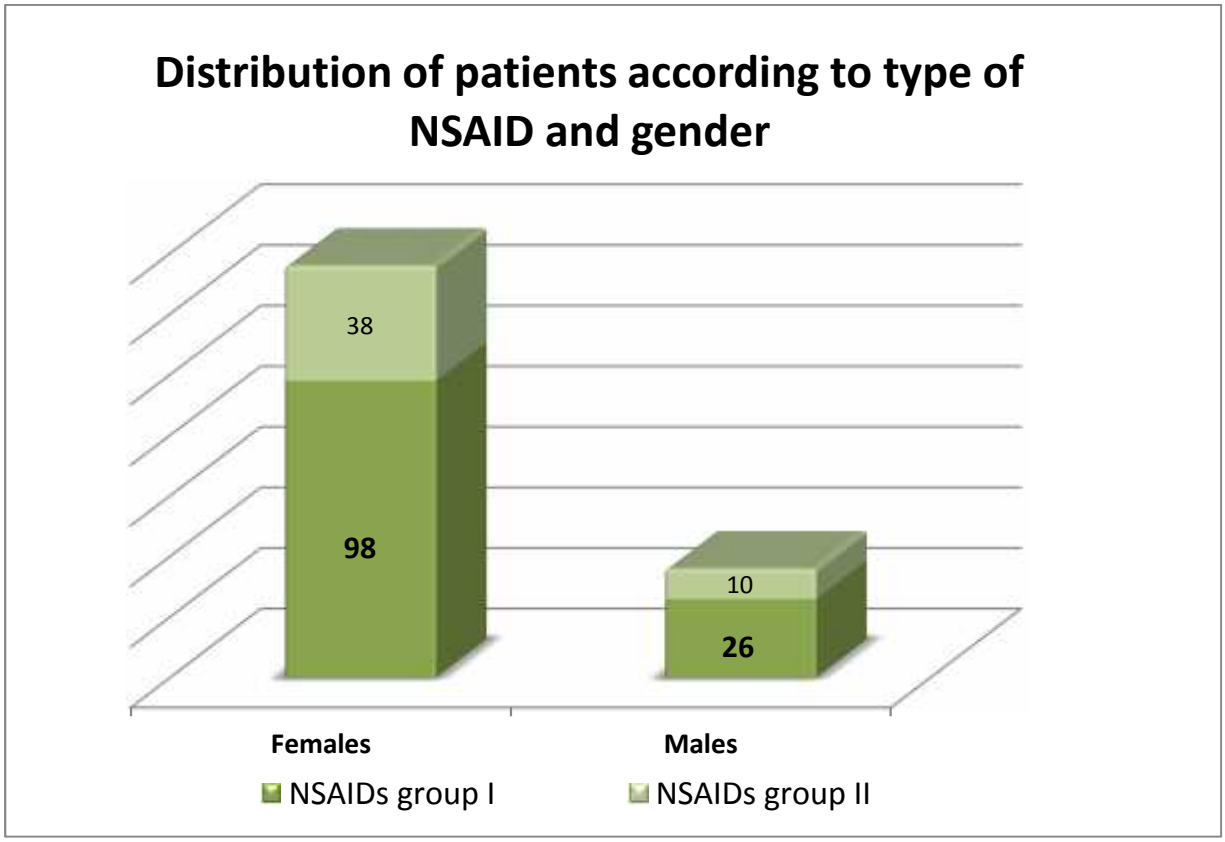

Figure 24. Distribution of patients according to type of NSAID and gender

C. Consumption of aspirin

Low-dose aspirin (75-100 mg/day), even up to 325 mg / day is widely used for the prevention of thrombotic cardiovascular disease. Its mechanism of action is irreversible inhibition of cyclooxygenase 1, so that powerful gastric adverse effects can occur. [57]

Aspirin is recognized as one of the leading causes of hospitalization for gastrointestinal bleeding. [58]

It is well known that aspirin, even in low doses increases the risk UGB. [59, 60]

Risk factors for chronic users of aspirin, even antiplatelet dose (75-100 mg / day) are:

- ≥70 years
- nonselective NSAID or coxibs comedication
- cotherapy with anticoagulants or antiplatelet drugs .[61]

However, in elderly patients with cardiovascular risk, when primary or secondary prophylaxis with low-dose aspirin is absolutely necessary, treatment may be associated with PPI (esomeprazole), this resulting in healing gastric mucosal lesions and prevent bleeding. [62]

Regarding the use of aspirin in the study group have met 123 consumers chronic low doses selected from the 143 patients with cardiovascular problems, meaning 95 women and 28 men.

Very important will be the further evaluation of the risk factors UGB, since accumulation of risk factors in patients from the study is great.

Gender	**ASA consumption**	
	Yes	No
Males	28	8
Females	95	41

Table 24. ASA consumption distribution by gender

The correlation between the consumption of NSAIDs and ASA gr I associated with symptoms

The table below shows the statistical correlation of symptoms in patients who used NSAIDs group I (non-selective), but concomitant aspirin.

Pain, heartburn, nausea and vomiting and bloating were not significantly correlated with the consumption of NSAID group I associated with aspirin.

Symptoms	**NSAIDs GR I + ASA**
Pain	0,278 (n=58)
Heartburn	0,299 (n=12)
Nausea and vomiting	0,136 (n=10)
Bloating	0,145 (n=8)
UGB	0,006 (n=11)

Table 25. Correlation of symptoms in the group of patients with associated consumption of NSAIDs + ASA group I

UGB incidence in users of NSAIDs group I was 8.87% (11 of 124 patients), as previously mentioned, while the concomitant use of aspirin in the same subset of patients increased the incidence UGB at 11.82 % (11 of 93 patients).

Although the incidence UGB did not correlate significantly only with the use of NSAIDs group I, combination with antiplatelet doses of aspirin in these patients has led to an increase of about 1.5 times its (statistically significant p = 0.006).

This is consistent with the literature, Laine et al. showing an increase of 2-5 times NSAIDs or low-dose ASA eaten separately. [63, 64]

The correlation between the consumption of NSAIDs and ASA group II associated with symptoms

Symptoms	**NSAIDs GROUP II+ASA**
Pain	0,857 (n=18)
Heartburn	0,069 (n=8)
Nausea and vomiting	0,438 (n=2)
Bloating	0,706 (n=1)
UGB	0,389 (n=1)

Table 26. Correlation of symptoms in the group of patients with associated consumption of NSAIDs + ASA group II

In The American Journal of Gastroenterology, Scheiman and colleagues reported results of a prospective randomized study on approximately 1400 patients with high gastrointestinal risk ,taking conventional NSAIDs or selective COX-2 inhibitors. Gastric complications occurred in 17.1% of patients taking traditional NSAIDs, respectively 16.5% of those taking selective COX-2. [65]

Although on the literature the association of aspirin to coxibs seems to cancel their gastroprotective effect, in our study UGB risk patients who used NSAIDs group II with low-dose aspirin was 3.33% (1 of 30 patients) than UGB risk patients consuming NSAIDs group I and aspirin -11.82% (11 of 90 patients).

This could be explained by the fact that most patients who used NSAIDs group I had high doses or combinations, representing a risk factor for the occurrence of UGB (9 of 11 UGB occurred at high doses or combinations of NSAIDs group I).

D. The use of oral anticoagulants

A retrospective study of elderly patients demonstrated a 3.3-fold increased relative risk in users of oral anticoagulants UGB, while the combination of oral anticoagulants with NSAIDs consumption leads to an increase of 12.7 times the relative risk of UGB. [66]

In the study group use of oral anticoagulants (acenocoumarol) occurred in a small number of patients - 5 women and 2 men (4.06%).

One of the 5 women diagnosed with atrial fibrillation, old myocardial infarction and post-thrombotic syndrome has chronic treatment with ASA and ACO, but not presented UGB.

E. The use of corticosteroids

Numerous epidemiological studies have shown that chronic consumption of systemic corticosteroids increase the risk of gastrointestinal complications of 1.1 to 2.2 times, while

their association with NSAIDs (particularly at high doses) increased risk of gastrointestinal complications (especially bleeding) 12-14 times compared to non-consumers. [67]

In our study group were 18 patients (10.46%) users of corticosteroids, 16 women and 2 men with AS/RA . Note they were intermittent consumers of corticosteroids (Medrol: 4-32 mg / day), ie during periods of disease activity. Also 13 patients (7.55%) , 6 women and 7 men were daily users of inhaled corticosteroids (fluticasone: 100-500 mg/day).

The correlation between the consumption of NSAIDs and corticosteroids associated symptoms

In the literature there are no studies showing the impact of steroid use on gastrointestinal symptoms in terms of growth rate, although the gastrotoxic effect of corticosteroids is well known.

Analyzing the influence of group I NSAIDs consumption associated with corticosteroids on symptoms, we noticed that a correlation cannot be established, probably because very few patients (2), but also because all of these patients had gastroprotective medications (pump inhibitors proton)

Analyzing the influence of group I NSAIDs consumption associated with corticosteroids on symptoms, we noticed that a correlation cannot be established, probably because very few patients (2), but also because all of these patients had gastroprotective medications (pump inhibitors proton)

Symptoms	**NSAIDs GROUP I+CS**
Pain	0,902 (n=1)
Heartburn	n=0
Nausea and vomiting	n=0
Bloating	n=0
UGB	0,699 (n=1)

Table 27. Correlation in the group of patients with symptoms associated with NSAID use I + CS group

Analyzing the influence of group I NSAIDs consumption associated with corticosteroids on symptoms, we noticed that a correlation cannot be established, probably because very few patients (2), but also because all of these patients had gastroprotective medications (pump inhibitors proton)

More patients in the study group, on treatment with corticosteroids, had associated NSAIDs group II (selective or specific), due to the fact that these patients had a diagnosis of rheumatoid arthritis or ankylosing spondylitis, and because NSAIDs group II are considered safer.

Symptoms	**NSAIDs GROUP II+CS**
Pain	0,049 (n=10)
Heartburn	n=0
Nausea and vomiting	0,059 (n=3)
Bloating	0,083 (n=2)
UGB	0,052 (n=1)

Table 28. Correlation in the group of patients with symptoms associated with NSAID consumption + CS group II

Although concomitant use of corticosteroids is an important risk factor for gastric complications from NSAIDs, this was not confirmed in our study (p = 0.052), although p was very close to have statistical significance, but statistically significantly correlated with stomach pain (p = 0.049).

F. Comorbidities

There are numerous studies in which the presence of associated diseases was considered an independent risk factor for gastric NSAIDs.

In the table below we have listed comorbidities that we encountered in the study group and the percentage that occurred each.

Comorbidities	**Males**	**Females**	**Total**	**Percentage**
Diabetes	6	14	20	11,62%
Cardiovascular diseases	24	119	143	83,14%
Hepatopathies	2	2	4	2,32%
Neoplasias	1	1	2	1,16%
COPD	7	6	13	7,55%
Osteoporosis	0	80	80	46,51%
Chronic renal failure	2	1	3	1,74%
Rheumatoid arthritis	0	16	16	9,30%
Anchilosing spondilitis	2	0	2	1,16%

Table 29. Distribution of comorbidities in the study group

A note should be made, namely that all patients of the study group were diagnosed with peripheral spinal osteoarthritis (BAVP), which is the main reason they were chronic users of NSAIDs, it met otherwise and literature. [68]

An impressive percentage of patients, respectively 92.44% (159 of 172 patients) had comorbidities (other than BAVP).

Cardiovascular diseases were the most frequent comorbidity was found in 119 women and 24 men. Of the 143 patients with cardiovascular impairment, 123 had chronic treatment with antiplatelet dose aspirin (75-100 mg / day).

In women the second most common comorbidity was osteoporosis, which is important from the perspective of osteoporotic treatment (bisphosphonates have potential gastrotoxic), followed by rheumatoid arthritis and diabetes.

In men other common comorbidities were COPD and diabetes.

Singh et al. recently proposed an algorithm based on the scoring summary that doctors and patients can use to estimate the risk of gastrointestinal complications with NSAIDs. If it is confirmed by other investigators, this tool could help to guide the specific NSAIDs prescriptions the prophylactic cotherapies or the necessity and frequency of monitoring patients. [69]

3.8. CORRELATION WITH VARIOUS RISK FACTORS

Correlation between pain and various risk factors

In elderly patients, chronic pain of various etiologies, including that of gastritis, is a very important symptom, major influencing quality of life.

For this reason, we considered it useful to see if it is associated with certain risk factors in terms of its prevalence in the presence or absence of potential risk factor, while the prevalence of pain in the general group was 58.13%.

We notice that the pain was significantly correlated with diabetes (p = 0.007), severe stress (p = 0.024), gastrotoxic drug consumption (p = 0.038) and positive HP infection (p = 0.024).

In our study, pain was not correlated with smoking (p = 0.760), pain frequency was even lower in smokers than in nonsmokers.

The same can be said about risk factors such as daily consumption of alcohol (p = 0.487), use of NSAID group I or II (p = 0.316), concomitant use of ASA (p = 0.232), corticosteroids (p = 0.213) or oral anticoagulants (p = 0.956).

Frequency of pain as onset symptom was still higher to daily users of alcohol, as well as to consumers ASA instead was similar in the presence or absence of concomitant use of corticosteroids or anticoagulants, and regardless of the type of NSAID used.

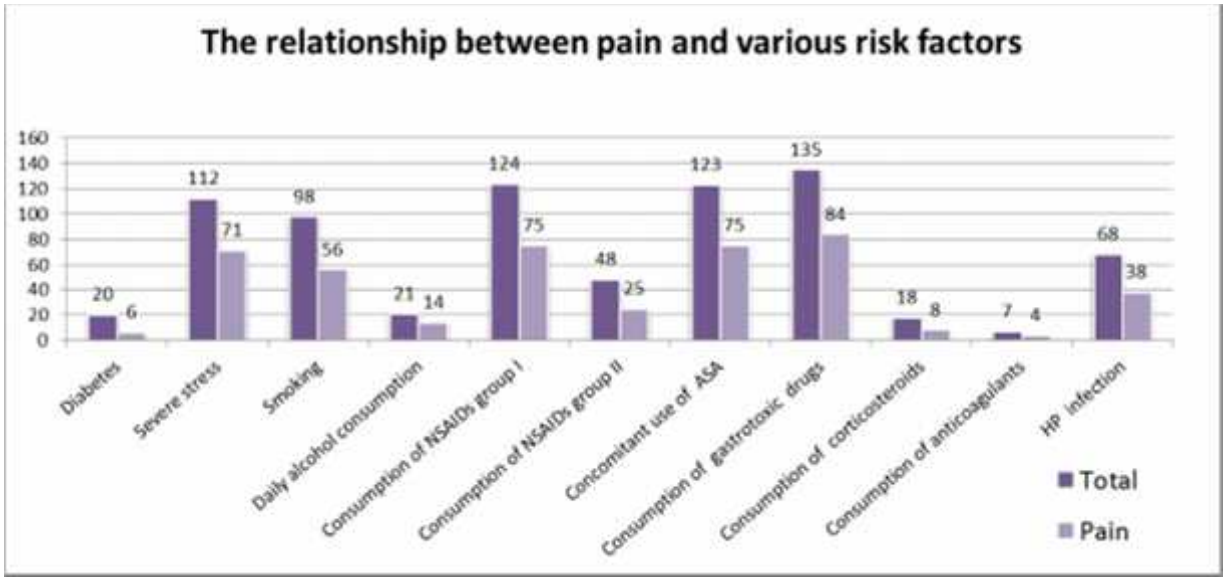

Figure 25. The relationship between pain and various risk factors

In the table below we present correlations between pain and the risk factors mentioned above.

Risk factors	Pain
Diabetes	0,007 (n=6)
Severe stress	0,024 (n=70)
Smoking	0,760 (n=55)
Daily consumption of alcohol	0,487 (n=14)
Consumption of NSAIDs group I	0,316 (n=74)
Consumption of NSAIDs group II	0,316 (n=26)
Concomitant use of ASA	0,232 (n=76)
Consumption of gastrotoxic drugs	0,038 (n=83)
Consumption of corticosteroids	0,213 (n=11)
Consumtion of anticoagulants	0,956 (n=4)
HP infection	0,024 (n=32)

Table 30. Statistical correlation of pain with various risk factors

The correlation between UGB and various risk factors

Among the risk factors that correlate with complications of NSAIDs (including UGB) remember age (as confirmed in our study), oral anticoagulants, corticosteroids, and / or ASA (12patients), high doses or combinations of NSAIDs (8 patients) and smoking, alcohol consumption, stress.

Severe stress and alcohol consumption were risk factors in patients UGB group (statistically significant p: 0.032 /0.048).

Upper GI bleeding is most important and most frequent complication of NSAIDs-induced gastritis in elderly, because its consequences (anemia, hypotension) and can lead to decompensation of associated diseases (heart failure, renal failure, COPD, liver failure ...)

Therefore we studied association with certain risk factors, comparing the prevalence of UGB in the presence or the absence thereof, provided that the study sample was prevalence of 6.97%.

Thus UGB was present at:

¬ 5% of those with diabetes (1 in 20 patients) and 7.23% of those without diabetes (11 of 152 patients)

¬ 10.71% of those with severe stress (12 of 112 patients), not present in any patient with moderate stress easily.

¬ 9.18% of smokers (9 of 98 patients) and 4.05% of smoking (3 of 74 patients)

¬ 19.04% of daily users of alcohol (4 of 21 patients) and 5.29% of nonconsumatori and occasional consumers (8 of 151 patients)

¬ 8.87% of consumers NSAID group I (11 of 124 patients) and 2.08% in group II NSAID consumers (1 of 48 patients).

We thought it useful and important to examine whether associations or high doses of NSAIDs group I influence the risk of UGB.

Thus, 20.93% of this subgroup (9 of 43 patients) experienced UGB, while therapeutic doses UGB was present in only 2.46% of users (3 of 81 patients)

¬ 6.66% of those with gastrotoxic drugs (9 of 135 patients) and 8.10% of those without gastrotoxic drugs (3 of 37 patients)

¬ 9.75% of consumers aspirin (12 of 123 patients), noting that all 12 cases of UGB were present to consumers ASA

¬ 11.11% of those who took corticosteroids (2 of 18 patients) and 6.49% of those who did not consume steroids (10 of 154 patients)

¬ 13.23% of those diagnosed with HP infection + (9 of 68 patients) and 3.77% of those diagnosed HP-(2 of 53 patients)

Note that these percentages were calculated for the 11 cases of UGB seen in the 151 patients who underwent rapid urease test for HP infection. A patient with UGB has not been investigated on HP infection

¬ 7.54% of patients with comorbidities (12 of 159 patients), noting that all 12 cases of UGB were recorded in patients with comorbidities.

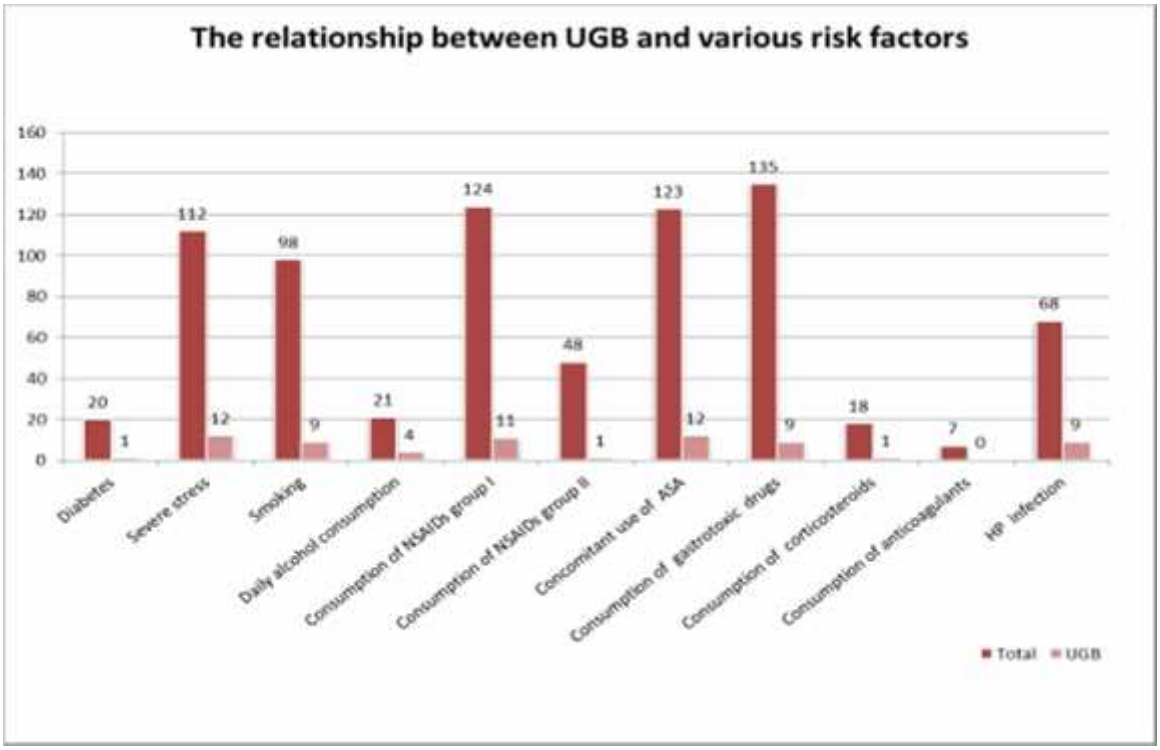

Figure 26. The relationship between UGB and various risk factors

Next we tried to analyze the correlation between UGB and the most important risk factors, mentioned in the literature.

Risk factors	UGB
Diabetes	0,712 (n=1)
Severe stress	0,032 (n=12)
Smoking	0,191 (n=9)
Daily alcohol consumption	0,048 (n=4)
Consumption of NSAIDs group I	0,117 (n=11)
Consumption of NSAIDs group II	0,117 (n=1)
Concomitant use of ASA	0.023 (n=12)

Consumption of gastrotoxic drugs	0,760 (n=9)
Consumption of corticosteroids	0,802 (n=1)
Consumption of anticoagulants	n=0
HP infection	0,031 (n=9)
Comorbidities	0,036 (n=12)

Table 31. UGB statistical correlation with various risk factors

We did not notice that the incidence of UGB was higher in the presence of diabetes mellitus, with no statistically significant correlation (p = 0.712).

Smoking patients showed an incidence of more than twice the UGB to smoking patients, but there is no statistically significant correlation (p = 0.191).

Although literature data are controversial, within our study group UGB was 4 times higher in group I patients than in group II patients (p = 0.117, not statistically significant).

All patients in our study group, with UGB, had therapy with low-dose aspirin, which is an important risk factor with statistically significant correlation (p = 0.023).

Gastrotoxic medication related, though significantly influenced pain, had no influence on the incidence of UGB (p = 0.760).

Use of corticosteroids concomitantly with NSAIDs caused a slight increase in the frequency of UGB without a statistically significant correlation (p = 0.802).

Although in the literature , concomitant use of oral anticoagulants with NSAIDs is an important risk factor for complications, we could not analyze this because no patient with UGB had associated oral anticoagulation.

In our study group the most important risk factors for the occurrence of UGB were age, as mentioned earlier (p = 0.001), daily alcohol consumption (p = 0.048) and severe stress (p = 0.032).

Also an important risk factor that significantly influenced UGB (p = 0.031) was within HP infection, increasing from about 4 times the risk of it than in patients without HP infection.

Although comorbidities (cardiovascular disease, COPD ...) were associated with increased risk of complications in some studies but not in others [1], in our study group comorbidities influenced the presence of UGB (p = 0.036).

The correlation between ulcers and various risk factors

Since endoscopic ulcerations were very common lesions in patients with upper GI bleeding, in our study, we considered useful to consider whether they were correlated with various risk factors.

Risk factors	Ulcerations
Diabetes	0,443 (n=5)
Severe stress	0,000 (54)
Smoking	0,179 (n=36)
Daily alcohol consumption	0,507(8)
Consumption of NSAIDs group I	0,002 (n=49)

Consumption of NSAIDs group II	0,002 (n=7)
Concomitant use of ASA	0,154 (44)
Consumption of gastrotoxic drugs	0,679 (n=45)
Consumption of corticosteroids	0,545 (n=7)
Consumption of anticoagulants	0,818 (n=2)
HP infection	0,078 (n=17)

Table 32. Statistical correlation with various risk factors ulcers

As seen in the table above, ulcers were not significantly correlated with any of the above risk factors.

However, ulceration correlated very strong statistically ($p < 0.001$) with severe stress and consumption of non-selective NSAIDs ($p = 0.002$).

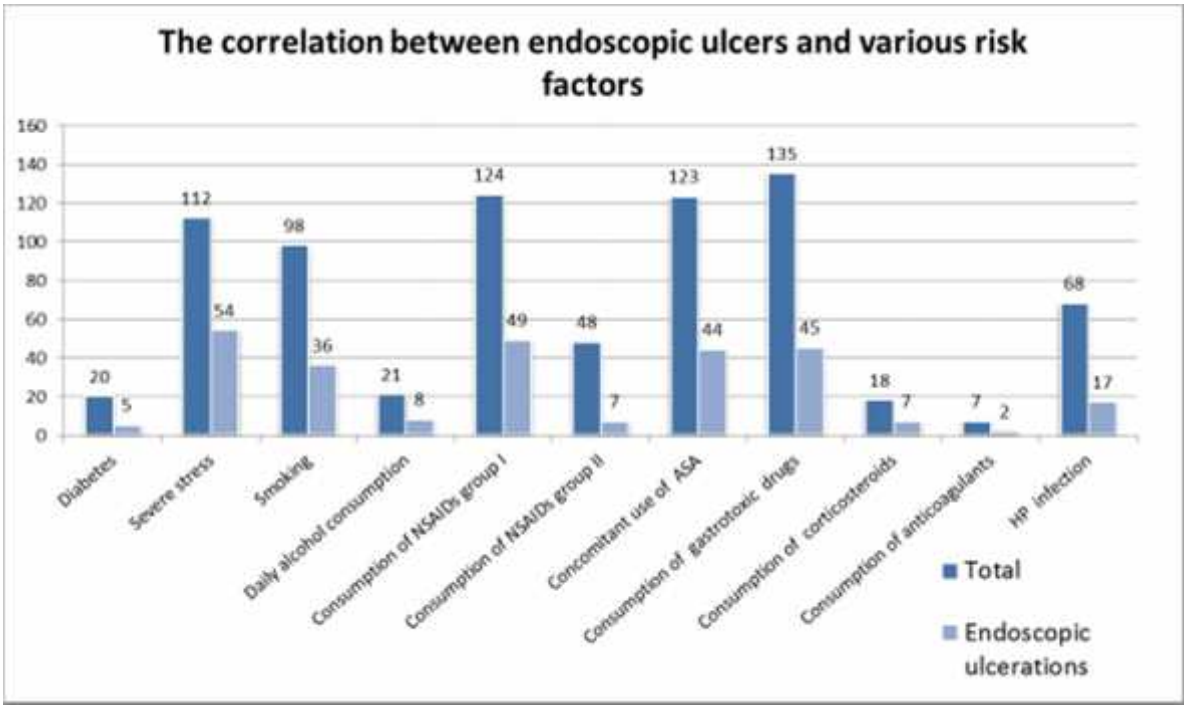

Figure 27. Relationship between ulceration and various risk factors

Correlation between epithelial erosions and various risk factors

Given that epithelial erosions were the most common histological lesions (44%) we considered useful to see if we can determine their correlation with risk factors listed in the table below.

Risk factors	Epithelial erosions –p (no patients)
Diabetes	0,574 (n=6)
Severe stress	0,006 (56)
Smoking	0,150 (n=37)
Daily alcohol consumption	0,818 (9)

Consumption of NSAIDs group I	0,935 (n=48)
Consumption of NSAIDs group II	0,935 (n=16)
Concomitant use of ASA	0,086 (n=44)
Consumption of gastrotoxic drugs	0,110 (n=52)
Consumption of corticosteroids	0,964 (n=6)
Consumption of antiacoagulants	0,225 (n=1)
HP infection	0,680 (n=27)

Table 33. Epithelial erosions statistical correlation with various risk factors

We note once again that severe stress, which influenced the incidence of pain, UGB and ulceration was significantly correlated with erosions (p = 0.006), being described as fundamental histopathological lesions in 50% of patients with severe stress (56 of 112 patients).

Correlation between hemorrhagic lesions (histological) and various risk factors

Hemorrhagic lesions were most severe histopathological lesions, being present in all 12 patients with upper GI bleeding.

Risk factors	Hemorrhagic lesions
Diabetes	0,871 (n=1)
Severe stress	0,119 (14)
Smoking	0,189 (n=11)
Daily alcohol consumption	0,059 (5)
Consumption of NSAIDs group I	0,327 (n=12)
Consumption of NSAIDs group II	0,327 (n=2)
Concomitant use of ASA	0,017 (14)
Consumption of gastrotoxic drugs	0,254 (n=9)
Consumption of corticosteroids	0,766 (n=1)
Consumption of antiacoagulants	n=0
HP infection	0,106 (n=10)

Table 34. Statistical correlation of hemorrhagic lesions with various risk factors

Although all 14 patients with hemorrhagic lesions showed severe stress there was a significant correlation with it, but not smoking, daily alcohol consumption, use of NSAID group I, combinations of drugs gastrotoxice or HP infection, as is observed in the table above.

The only statistically significant correlation was with concomitant low-dose aspirin (p = 0.017).

From this perspective, elderly patients should carefully evaluated from the point of view of the cardiovascular and gastrointestinal risk, so that small doses of aspirin NSAIDs should be given especially while mean a benefit for the patient. [97]

Upper GI bleeding is the most important complication in the study group, as in the literature. Taking into account all risk factors under consideration, as well as correlations set, I tried to outline profile of elderly patients with high risk of complications.

In the table below, we have grouped the demographic, environmental and lifestyle origin of the subgroup of patients with UGB.

We note that there was no difference in terms of sex, most patients were from rural areas, patients were aged over 75 years (mean age 84.58 ± 4.660) and lifestyle significantly influenced UGB appearance.

Characteristics		**Patients with UGB (n=12)**
Males: females		5:7
Medium of origin (urban:rural)		2:10
Mean ages of patients (average±sd)		84,58 (± 4,660)
Age groups	65-74 years	0
	75-84 years	6
	≥85 years	6
Stress severe		12
Smoking		9
Alcohol consumption		4

Table 35. Demographic characteristics, environmental and lifestyle origin of subgroup with UGB

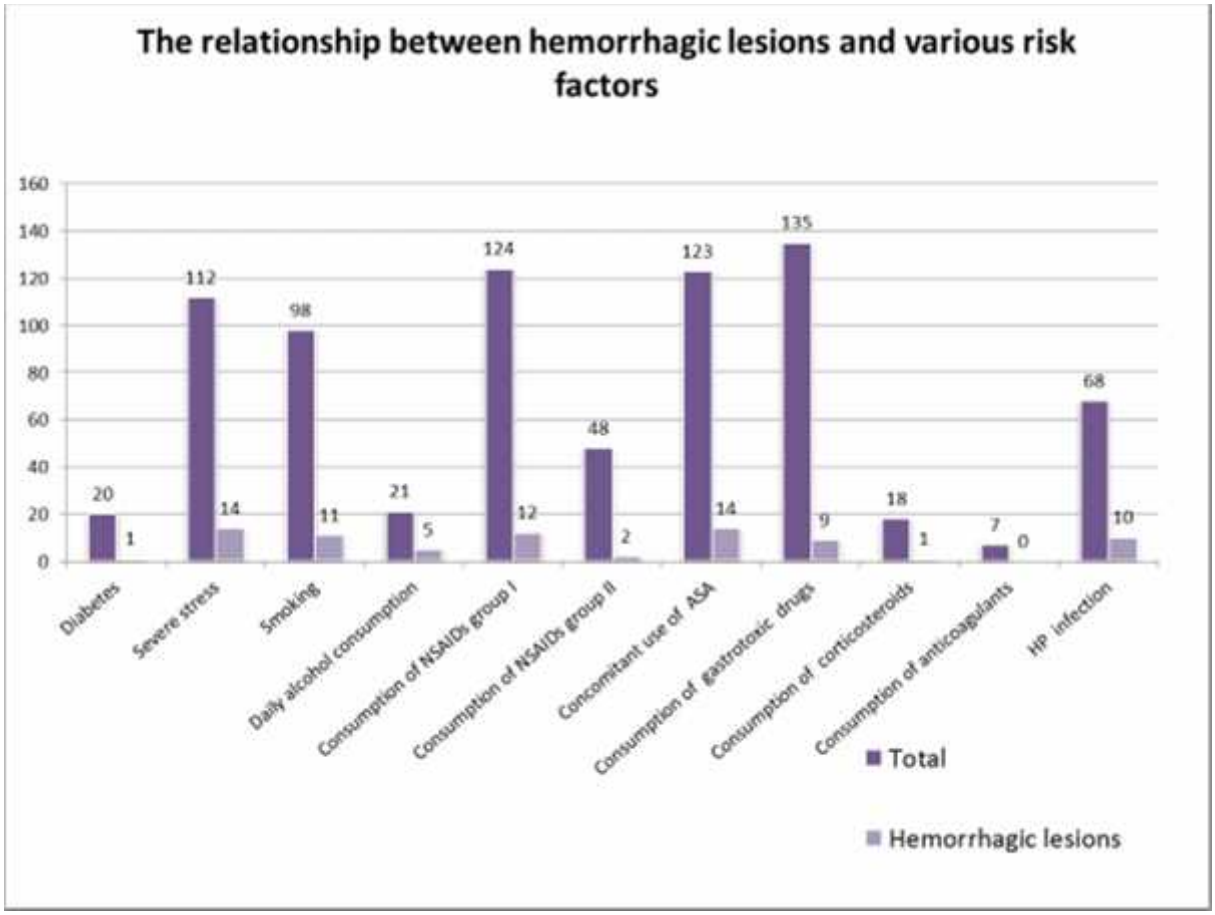

Figure 28. The relationship between hemorrhagic lesions and various risk factors

Next we analyzed by logistic regression risk factors for UGB

Risk factors for UGB (logistic regression)	R^2
Smoking	0,353
Alcohol consumption	0,149
Endoscopic ulcerations	0,000
Hemorrhagic lesions (histopathological examination)	0,000
NSAIDs group I	0,159
NSAIDs group II	0,159
Concomitant ASA use	0,029
HP infection	0,080

Table 36. Risk factors for UGB (logistic regression)

From this analysis it appears that predictive variables with a greater value are endoscopic ulceration, hemorrhagic lesions and concomitant use of ASA.

However each of the selected independent variables (smoking, alcohol, ..., HP infection) contributes to the variation of the dependent variable (in our group UGB) in a certain percentage, but as we have seen, not all statistically significant influence.

CHAPTER4. CONCLUSIONS

1. Consumption of NSAIDs are the most common cause of gastritis in elderly patients (56.21%).

2. Age is an important risk factor of gastritis (63.75% in group initially selected were patients over 65, compared to 36.24% of patients under 65 years)

3. Pain (refractory to conservative treatment with gastric antisecretory and strong enough to require hospitalization) was the most common symptom, so the whole group (58.13%) and for each age group. Identified risk factors for pain were: diabetes mellitus, severe stress and concomitant corticosteroid use and specific selective NSAIDs.

4. UGB risk factors were: age, severe stress, daily consumption of alcohol, the concomitant use of aspirin (especially associated with non-selective NSAIDs) and comorbidities. Upper gastrointestinal bleeding had a higher incidence in the study group - 6.97%, peaking at 30% in the very elderly (over 85 years).

5. In our study, HP infection was significantly correlated with pain and UGB. The incidence of HP infection subgroup undergoing rapid urease test was 56.19% (consistent with data from the literature).

6. Risk factors for severe endoscopic lesions (ulcers) were severe stress and consumption of non-selective NSAIDs.

7. Risk factors identified for histopathological lesions were represented by severe stress for epithelial erosions and concomitant use of aspirin to bleeding lesions.

8. In terms of clinical and endoscopic, pain was significantly correlated with endoscopic erosions and upper gastrointestinal bleeding with erythema and ulceration.

9. Clinical and histopathologic correlations in the study group were statistically significant: heartburn and epithelial erosions, pain and bleeding lesions and highly statistically significant for UGB and hemorrhagic lesions and malignancy.

10. In terms of correlation between endoscopic and histopathological lesions, the following associations were statistically significant: endoscopic erosions with epithelial erosions, hyperplasia foveolară and edema, erythema with erosions epithelial hyperplasia foveolară and swelling, and bleeding lesions and ulcerations foveolară hyperplasia and edema.

11. The presence of two cancer cases (2%) detected on histopathology unchanged endoscopic supports the idea that, in elderly patients, it is better to exclude this possibility by any means, including gastric biopsies.

12. In our study group, habits and lifestyle risk factors were more important than the use of oral anticoagulants and corticosteroids. Daily alcohol consumption can significantly influence the UGB and severe stress influence both pain and UGB.

13. The incidence of complications in the elderly requires a comprehensive assessment of its risk in terms of both gastrointestinal and cardiovascular of one and the opportunity of using NSAIDs to be carefully weighed the risk-benefit perspective. When NSAID use is absolutely necessary, must take all primary and secondary prevention measures.

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