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Significance of Risk Factors for Nonsteroidal Anti-Inflammatory Drug-Induced Gastropathy in Patients with Rheumatoid Arthritis

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Aim: to determine the frequency of detection of nonsteroidal anti-inflammatory drug-induced (NSAID-induced) gastropathy in patients with rheumatoid arthritis depending on risk factors.
Materials and methods. A total of 97 patients with rheumatoid arthritis were examined. The control group consisted of 35 virtually healthy individuals who did not take NSAIDs and were matched for age and sex with the main group. A questionnaire survey was conducted to evaluate seven risk factors (one point for a positive response). All patients underwent esophagogastroduodenoscopy with the assessment of gastropathy severity using the F.L. Lanza scale for quantitative evaluation of erosive and ulcerative lesion severity.
Results. The analysis showed that the number of patients with rheumatoid arthritis who had no risk factors was small and amounted to 7 individuals (7.2 % of the total number of patients in the group). At the same time, gastropathy was detected in 5 (71.4 %) cases even among these individuals. Gastropathy was detected in 73 (81.1 %) out of 90 patients with ≥ 1 risk factor, but the difference with the group without risk factors was statistically insignificant (χ^2 = 0.39; p > 0.05; odds ratio (OR) = 1.718; 95% confidence interval (95% CI): 0.307–9.618). In the group of patients with ≥ 2 risk factors, gastropathy was detected in 70 (84.3 %) out of 83 patients; the difference with the group with ≤ 1 risk factor was statistically significant (χ^2 = 5.62; p < 0.05; OR = 4.038; 95% CI: 1.201–13.581). In patients with ≥ 3 risk factors, gastropathy was detected in 58 (89.2 %) out of 65 cases; the difference with the group with ≤ 2 risk factors was statistically significant (χ^2 = 9.73; p < 0.05; OR = 4.971; 95% CI: 1.719–14.374).
Conclusions. The calculation of the odds ratio with a 95% confidence interval shows that the absence of risk factors does not exclude the presence of gastropathy in a patient; however, the risk of its development increases statistically significantly with the accumulation of two or more factors.
Keywords: nonsteroidal anti-inflammatory drugs, gastropathy, rheumatoid arthritis, risk factors
Conflict of interest: the authors declare no conflicts of interest.

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Значимость факторов риска гастропатии, индуцированной нестероидными противовоспалительными препаратами, у пациентов с ревматоидным артритом

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Цель: определить частоту выявления гастропатии, индуцированной нестероидными противовоспалительными препаратами (НПВП), у больных ревматоидным артритом в зависимости от факторов риска.
Материалы и методы. Обследовано 97 пациентов с ревматоидным артритом. Контрольную группу составили 35 практически здоровых человек, не принимающих НПВП, сопоставимых по возрасту и полу с основной группой. Проведено анкетирование с оценкой семи факторов риска (по одному баллу за положительный ответ). Всем пациентам была выполнена эзофагогастродуоденоскопия с определением выраженности гастропатии по шкале F.L. Lanza для количественной оценки тяжести эрозивно-язвенного процесса.
Результаты. Анализ показал, что число пациентов с ревматоидным артритом, не имевших факторов риска, было невелико и составило 7 человек (7,2 % от общего числа пациентов в группе). В то же время и среди этих лиц была выявлена гастропатия в 5 (71,4 %) случаях. Гастропатия выявлена у 73 (81,1 %) из 90 пациентов, имеющих ≥ 1 фактора риска, но разница с группой, не имевшей факторов риска, оказалась статистически незначимой (χ^2 = 0,39; p > 0,05; отношение шансов (ОШ) — 1,718; 95% доверительный интервал (95% ДИ): 0,307–9,618). В группе пациентов, имевших ≥ 2 факторов риска, гастропатия выявлена у 70 (84,3 %)

из 83 пациентов, при этом разница с группой, имевшей ≤ 1 фактора риска, оказалась статистически значимой (χ^2 = 5,62; p < 0,05; ОШ = 4,038; 95% ДИ: 1,201–13,581). У пациентов, имеющих ≥ 3 факторов риска, гастропатия выявлена в 58 (89,2 %) из 65 случаев, при этом разница с группой, имевшей ≤ 2 факторов риска, оказалась статистически значимой (χ^2 = 9,73; p < 0,05; ОШ = 4,971; 95% ДИ: 1,719–14,374).
Выводы. Расчет отношения шансов с 95% доверительным интервалом показывает, что отсутствие факторов риска не исключает наличие у пациента гастропатии, однако риск ее развития статистически значимо возрастает при накоплении двух и более факторов.
Ключевые слова: нестероидные противовоспалительные препараты, гастропатия, ревматоидный артрит, факторы риска
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in rheumatoid arthritis [1]. However, despite their high efficacy, these medications have a number of adverse side effects that significantly limit their use [2].

NSAID-induced gastropathy is the most common and well-studied complication associated with NSAID use, which frequently occurs in rheumatoid arthritis and poses a threat to the lives of these patients.

The development of the pathology is largely associated with the presence of risk factors in the patient: age over 65 years, smoking, history of peptic ulcer and its complications, history of gastrointestinal bleeding of any etiology, concomitant use of systemic corticosteroids and antithrombotic drugs (antiplatelets and anticoagulants) with acetylsalicylic acid and/or other NSAIDs, as well as Helicobacter pylori infection [2, 4].

Preliminary analysis of risk factors before the initiation of therapy, as well as early implementation of preventive and therapeutic measures, are of great importance and highly relevant in clinical practice.

Aim of the study: to determine the frequency of detection of gastropathy in patients with rheumatoid arthritis depending on the number of risk factors.

Materials and methods

A total of 97 patients with rheumatoid arthritis were examined at the clinical base of Lugansk State Medical University named after Saint Luka of the Ministry of Health of the Russian Federation — in the rheumatology department and the rheumatology room of the clinic of Lugansk Republican Clinical Hospital of the LNR.

Inclusion criteria: a verified diagnosis of rheumatoid arthritis in accordance with the criteria of the Association of Rheumatologists of Russia (2024); NSAID use at the time of inclusion in the study [5, 6].

Exclusion criteria: use of proton pump inhibitors and/or cytoprotectors (in particular, bismuth preparations and/or rebamipide) within 2 weeks prior to inclusion in the study.

The study was performed in accordance with the principles of the Declaration of Helsinki of the World Medical Association and approved by the local independent ethics committee of Lugansk State Medical University named after Saint Luka of the Ministry of Health of the Russian Federation (Minutes No. 3 dated November 21, 2023).

All patients underwent a questionnaire survey using the developed questionnaire (Table 1). The structure of the questionnaire included two main diagnostic blocks. The first block (questions 1–6) was designed to calculate the symptom score (SS) by summing the number of days per week during which the patient experienced dyspeptic symptoms. The second block (questions 7–13) aimed to evaluate seven classic risk factors for the development of NSAID-induced gastropathy approved in clinical guidelines. For each positive response in this block, 1 point was awarded, and for a negative response, 0 points. In question No. 9, which evaluated *Helicobacter pylori* infection status, a point was assigned when choosing one of three response options confirming the presence of the infection. The maximum score on the risk factor scale was 7 points. Additionally, demographic data (age), smoking status of the patient, and the nature of concomitant therapy (questions 14–18) were recorded in the questionnaire.

All patients underwent esophagogastroduodenoscopy (EGD) to detect gastropathy (EG-290Kp video gastroscope, Pentax, Japan). During EGD, the severity of gastropathy was determined using the modified F.L. Lanza scale [7, 8] for further

Table 1. Structure of the developed questionnaire for rapid assessment of dyspeptic symptoms and risk factors for NSAID-induced gastropathy

Questionnaire No.					
Date	Visit No. 1:		Visit No. 2:		
Sex		Age			
Smoking: yes/no		Smoking experience			
Enter in the cell the number corresponding to the number of days during the past week when you experienced the symptom specified in the question					
1.	Have you experienced a feeling of abdominal bloating (in the middle of the abdomen above the navel)?				
Visit No. 1:		Visit No. 2:			
2.	Have you experienced belching of air or food?				
Visit No. 1:		Visit No. 2:			
3.	Have you experienced a feeling of postprandial abdominal heaviness?				
Visit No. 1:		Visit No. 2:			
4.	Have you experienced a feeling of early satiety (a sensation of "fullness" during meals)?				
Visit No. 1:		Visit No. 2:			
5.	Have you experienced abdominal pain (in the middle of the abdomen above the navel)?				
Visit No. 1:		Visit No. 2:			
6.	Have you experienced an abdominal burning sensation (in the middle of the abdomen above the navel)?				
Visit No. 1:		Visit No. 2:			
TOTAL: Symptom Score (SS)					
Visit No. 1:		**Visit No. 2:**			
Answer the questions by marking the "Yes" cell with a "+" sign if the statement specified in the question is true for you. Where applicable, enter the name of the medication if you do not see it among the options.					
7.	Do you have gastric and/or duodenal ulcer disease?				
Yes		No			
8.	Have you ever experienced an episode of gastrointestinal bleeding in your lifetime?				
Yes		No			
9.	Do you know whether you have a *Helicobacter pylori* infection?				
I do not know, never tested	I know I have it	I know I do not have it	Underwent *H. pylori* eradication therapy, repeat test was not performed	Underwent *H. pylori* eradication therapy, repeat test was positive (infection persists)	Underwent *H. pylori* eradication therapy, repeat test was negative (infection eradicated)
10.	Do you regularly take medications from the glucocorticoid group (Medrol, Metypred, etc.)?				
Yes		No			
11.	Do you regularly take acetylsalicylic acid medications (Aspirin Cardio, Thrombo ASS, Cardiomagnyl, Aspicard, CardiASK, etc.)?				
Yes		No			
12.	Do you regularly take medications from the anticoagulant group, also known as "blood thinners" (Eliquis, Xarelto, Pradaxa)?				
Yes		No			
13.	Do you regularly take medications from the antithrombotic group, also known as "blood thinners" (Clopidogrel, Plavix, Lopirel, etc.)?				
Yes		No			
Enter in the cell the number of "Yes" responses to questions 7–13 (for question No. 9, any of the underlined options is considered a "Yes" response)					
TOTAL Risk Factors (RF)					
14.	Do you regularly take medications to lower blood pressure with names ending in -pril (enalapril, lisinopril, ramipril, etc.)? (if "yes", underline/write _____ the name of the medication)				
Yes		No			

15.	Do you take medications from the nonsteroidal anti-inflammatory group regularly and/or within the past 2 weeks to manage joint pain: nimesulide (Nise, Nimesil, etc.), ibuprofen (Nurofen, etc.), diclofenac (Voltaren, Naklofen Duo, etc.), meloxicam (Movalis, Amelotex, etc.), ketoprofen (Artrosilen, Flamax, etc.), dexketoprofen (Dexalgin, etc.), etoricoxib (Arcoxia, etc.), celecoxib (Celebrex, etc.), lornoxicam (Xefocam, etc.), naproxen (Nalgesin, Theralive, etc.), etc.? (if "yes", underline/write _____ the name of the medication) (EXCLUDING topical forms — gels/ointments)		
Yes		No	
16.	Do you regularly take medications that reduce stomach acid: omeprazole (Omez, etc.), rabeprazole (Razo, etc.), lansoprazole (Lanzap, etc.), esomeprazole (Emanera, etc.), pantoprazole (Nolpaza, etc.)? (if "yes", underline the name of the medication)		
Yes		No	
17.	Have you taken medications that reduce stomach acid within the past 2 weeks: omeprazole (Omez, etc.), rabeprazole (Razo, etc.), lansoprazole (Lanzap, etc.), esomeprazole (Emanera, etc.), pantoprazole (Nolpaza, etc.), ranitidine, famotidine, bismuth preparations (De-Nol, Vicair, etc.)? (if "yes", underline the name of the medication)		
Yes		No	
18.	Have you taken rebamipide (Rebagit, etc.) within the past two weeks?		
Yes		No	
INTERPRETATION OF RESULTS			
Symptom Score (SS)			
10–14 points — moderate risk of NSAID-induced gastropathy — EGD is not recommended; 15–19 points — high risk of NSAID-induced gastropathy — EGD according to individual indications, including assessment of the presence of risk factors; ≥ 20 points — very high risk of NSAID-induced gastropathy — EGD is recommended			
Risk Factors (RF)			
2 points — moderate risk of NSAID-induced gastropathy — EGD according to individual indications, including assessment of the symptom score; ≥ 3 points — high risk of NSAID-induced gastropathy — EGD is recommended			

Note: *EGD — esophagogastroduodenoscopy.*

quantitative evaluation of the severity of the erosive and ulcerative process:

- 0 points — absence of hemorrhages or erosions;
- 1 point — single hemorrhages;
- 2 points — presence of 1 to 2 erosions;
- 3 points — presence of 3 to 10 erosions;
- 4 points — presence of more than 10 erosions or an ulcer.

The control group consisted of 35 virtually healthy individuals who did not take NSAIDs and were matched for age and sex with the patients of the main group.

Statistical analysis of the results was performed using the Statistica 10 software package (StatSoft Inc., USA), including commonly accepted methods of parametric and nonparametric analysis. Qualitative variables were described by absolute and relative frequencies (percentages). When studying the patient questionnaire data, Pearson's chi-squared test (χ^2) was used to evaluate the statistical significance of differences between the groups. To evaluate the association between a certain number of points scored and the development of gastropathy, the odds ratio (OR) with a 95% confidence interval (95% CI) was calculated. Differences were considered statistically significant at $p < 0.05$. All stages of the study were conducted in accordance with legislation and regulatory documents. Voluntary informed consent was obtained from all patients included in the study.

Results

EGD data on the distribution of patients by the severity of NSAID-induced gastropathy according to the F.L. Lanza scale are presented in Table 2.

As shown in the table, 19 (19.6 %) out of 97 examined patients had no endoscopic signs of NSAID-induced gastropathy. NSAID-induced gastropathy was confirmed by EGD in 78 (80.4 %) patients. Single hemorrhages were found in 15 (15.5 %) patients. More than half of the examined patients (56.7 %) had 1 to 10 erosions: 1–2 erosions were observed in 26 (26.8 %) and 3–10 erosions in 29 (29.9 %) patients. More than 10 erosions were detected in 8 (8.2 %) patients, while ulcers were not found in any of the study participants.

Data on the distribution of patients by the number of risk factors and the presence of NSAID-induced gastropathy, indicating the odds ratio

Table 2. Distribution of main group patients ($n = 97$) by the severity of NSAID-induced gastropathy during esophagogastroduodenoscopy

Indicators	Gastropathy is not detected	The severity of NSAID-induced gastropathy (points)			
	0	1	2	3	4
Number of patients, *n* (%)	19 (19.6 %)	15 (15.5 %)	26 (26.8 %)	29 (29.9 %)	8 (8.2 %)

Table 3. Distribution of main group patients by the number of risk factors and the presence of NSAID-induced gastropathy

Number of risk factors	Number of patients	Gastropathy is detected	Gastropathy is not detected	χ^2	OR (95% CI)
0	7	5 (71.4 %)	2 (28.6 %)	–	–
1 and more	90	73 (81.1 %)	17 (18.9 %)	0.39	1.718 (0.307–9.618)
2 and more	83	70 (84.3 %)	13 (15.7 %)	5.62*	4.038 (1.201–13.581)
3 and more	65	58 (89.2 %)	7 (10.8 %)	9.73*	4.971 (1.719–14.374)

Note: ** — differences are statistically significant ($p < 0.05$); OR — odds ratio; CI — confidence interval.*

(OR) of its development depending on the number of risk factors, are presented in Table 3.

As shown in Table 3, the number of patients with rheumatoid arthritis who had no risk factors was very small — 7 individuals, or 7.2 % of the total number of examined patients. At the same time, NSAID-induced gastropathy was detected in 5 (71.4 %) cases even among these patients. In the group with ≥ 1 risk factor, gastropathy was detected in 73 (81.1 %) out of 90 patients, but the difference with the group without risk factors was statistically insignificant ($\chi^2 = 0.39$; $p > 0.05$; OR = 1.718; 95% CI: 0.307–9.618). In the group of 83 patients with ≥ 2 risk factors, NSAID-induced gastropathy was detected in 70 (84.3 %) cases, with the difference with the group with ≤ 1 risk factor being statistically significant ($\chi^2 = 5.62$; $p < 0.05$; OR = 4.038; 95% CI: 1.201–13.581). In patients with ≥ 3 risk factors, NSAID-induced gastropathy was detected in 58 (89.2 %) out of 65 cases, with the difference with the group with ≤ 2 risk factors being statistically significant ($\chi^2 = 9.73$; $p < 0.05$; OR = 4.971; 95% CI: 1.719–14.374).

The frequency of detection of NSAID-induced gastropathy in patients with varying numbers of risk factors is presented in Figure 1.

Data on the distribution of control group patients by the number of risk factors and the presence of NSAID-induced gastropathy are presented in Table 4.

As shown in Table 4, NSAID-induced gastropathy was detected in a total of 7 (20.0 %) out of 35 control group patients. At the same time, 23 (65.7 %) patients had no risk factors, 6 (17.1 %) individuals had 1 risk factor each, and another 6 (17.1 %) had 2 risk factors each. None of the control group individuals had more than 2 risk factors. Among the control group patients without risk factors, NSAID-induced gastropathy

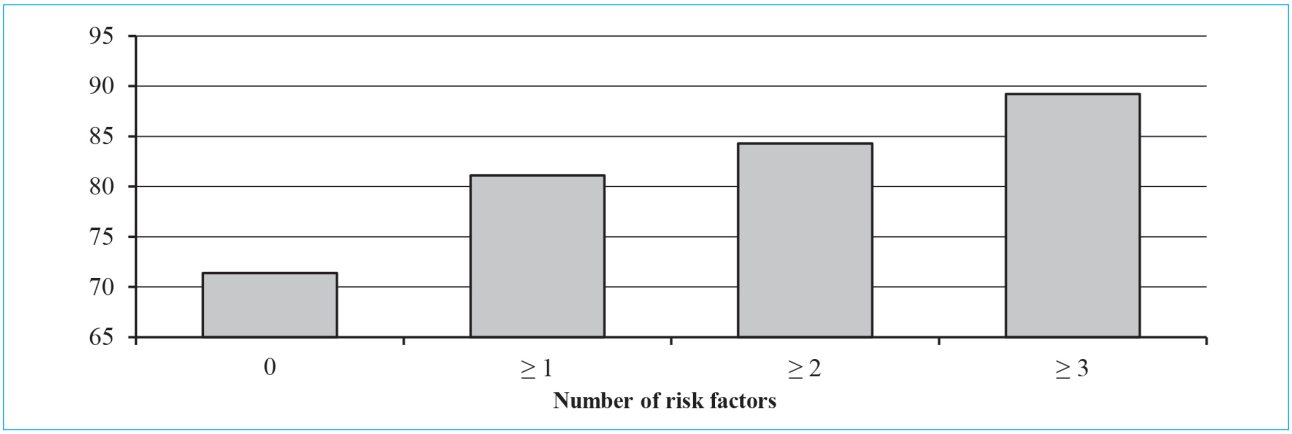

Figure. The frequency of detection of NSAID-induced gastropathy depending on the number of risk factors (%)

Table 4. Distribution of control group patients (n = 35) by the number of risk factors and the presence of NSAID-induced gastropathy

Number of risk factors	Number of patients	Gastropathy is detected (%)	Gastropathy is not detected (%)
0	23	3 (13.0 %)	20 (87.0 %)
1	6	2 (33.3 %)	4 (66.7 %)
2	6	2 (33.3 %)	4 (66.7 %)

was detected by EGD in 3 (13.0 %) cases; among those with 1 and 2 risk factors, it was found in 2 (33.3 %) out of 6 patients in both subgroups.

Thus, among the main group patients without risk factors, NSAID-induced gastropathy was detected in 71.4 % of cases. Among patients with ≥ 1 risk factor, NSAID-induced gastropathy was found in 81.1 % of cases, but the difference with the group without risk factors was statistically insignificant. In the group with ≥ 2 risk factors, NSAID-induced gastropathy was detected in 70 (84.3 %) out of 83 patients, with the difference with the group with ≤ 1 risk factor being statistically significant. In patients with ≥ 3 risk factors, NSAID-induced gastropathy was found in 89.2 % of cases, with the difference with the groups with ≤ 1 risk factor and ≤ 2 risk factors being statistically significant. In the control group individuals, NSAID-induced gastropathy was detected in 7 (20.0 %) out of 35 cases. At the same time, 65.7 % had no risk factors, 17.1 % had 1 risk factor, and another 17.1 % had 2 risk factors.

The calculation of the odds ratio with a 95 % confidence interval shows that the accumulation of two or more risk factors is statistically significantly associated with the development of NSAID-induced gastropathy in patients with rheumatoid arthritis.

Discussion

Risk factors for gastrointestinal diseases are well known [2, 4, 9]. The lists of these factors, as defined in scientific publications and clinical guidelines on this topic, comprehensively cover the etiopathogenetic characteristics of NSAID-induced gastropathies [2, 8–10]. However, the significance of individual predictors of NSAID-induced gastropathies remains undetermined and is therefore underestimated by clinicians. The analysis of risk factors is particularly important at present, when the additional examination of patients with gastroenterological symptoms in a rheumatology clinic is difficult. Moreover, physicians should also consider patient compliance, as patients are focused on treating the underlying disease. Under these conditions, the analysis of the significance of risk factors becomes highly relevant for both the patient and the treating physician.

The use of NSAIDs, an essential class of medications in rheumatoid arthritis, significantly increases the risk of gastric lesions [10], which was confirmed in our study. It was found that the number of patients with rheumatoid arthritis (receiving NSAID therapy) who had no risk factors was very small. However, the majority of such patients were diagnosed with NSAID-induced gastropathy. Data obtained by other researchers demonstrate a relationship between the number of risk factors and the frequency of NSAID-induced gastropathy development [2]. Our study showed a significant increase in the risk of developing the pathology in patients with rheumatoid arthritis with ≥ 2 risk factors, with the detection rate exceeding 84 %, while a further increase in the number of risk factors was accompanied by an increase in this indicator to 89.2 %.

The data obtained in the control group are also important. Thus, the endoscopic examination showed that in the vast majority of virtually healthy individuals without risk factors, NSAID-induced gastropathy was absent (in 87.0 % of cases).

Conclusion

1. The presence of two or more risk factors in patients with rheumatoid arthritis is associated with the development of NSAID-induced gastropathy in 84.3 % of cases, which determines the need for therapeutic and preventive measures.
2. An increase in the number of risk factors increases the frequency of detection of NSAID-induced gastropathy; in the presence of three or more risk factors, it reaches 89.2 %.

The analysis of the obtained results showed that the presence of two or more risk factors warrants therapeutic and preventive measures to prevent NSAID-induced gastropathy in patients with rheumatoid arthritis. However, the detection of characteristic signs of NSAID-induced gastropathy in patients without risk factors and in certain healthy individuals requires further studies with an expanded sample size and, possibly, the search for new, more universal risk factors.

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