

# Risk Factors Associated with Gastrointestinal Complications Caused by Nonsteroidal Anti-Inflammatory Drugs (NSAID)

Viola Cala<sup>1\*</sup>, Floreta Kurti<sup>2</sup>, Elizana Petrela<sup>3</sup>, Elona Mollsi<sup>4</sup>

<sup>1</sup> Service of Radiology, University Hospital Center “Mother Theresa” Tirana, Albania

<sup>2</sup>Service Gastrohepatology, University Hospital Center “Mother Theresa” Tirana, Albania

<sup>3</sup>Service of Statistics, University Hospital Center “Mother Theresa” Tirana, Albania

<sup>4</sup>Faculty of Medical Technical Science “Aleksander Xhuvani”, Elbasan, Albania

---

## Abstract

**Background:** Nonsteroidal anti-inflammatory drugs (NSAIDs) are a significant cause of emergency hospitalizations and death. This study aimed to identify the most common risk factors associated with complicated gastrointestinal bleeding and/or complicated peptic ulcer caused by NSAIDs.

**Aim:** Our study aimed to know more about the risk factors associated with gastrointestinal complications caused by NSAIDs in the elderly population.

**Material and methods:** We have retrospectively evaluated the medical files of patients hospitalized at the General Surgery Service, University Hospital Center “Mother Theresa” Tirana, Albania with the diagnosis gastrointestinal bleeding (GIB) or peptic ulcer

for ten years, from 2011 until 2021. We evaluated 307 patients hospitalized with these diagnoses who had used NSAID or corticosteroids to treat rheumatic pathologies. We considered age, gender, family and personal history of peptic ulcer, concomitant diseases, medications used, and their duration for all patients.

**Results:** We identified 260 females (85.2%) and 45 males (14.8%), with a mean age of 68.4 years (SD +13.4). Ninety of the patients (29.5%) had used antiplatelet drugs as concomitant cardiovascular and cerebrovascular diseases in which, 37 patients (35.9%) of this group were with peptic ulcer and 53 patients (26.2%) were with GIB ( $p = 0.05$ ).

Fifty-nine patients (19.3%) had used cortisone for rheumatic disease, in which 13 patients (12.6%)

**Address for correspondence:** Viola Cala\*, Service of Radiology, University Hospital Center “Mother Theresa” Tirana, Albania. Email: violacala08@gmail.com

were with peptic ulcer and 46 patients (22.8%) were with GIB ( $p = 0.034$ ).

One hundred twenty-five patients (78.1%) were diagnosed with Diabetes Mellitus (DM), 43 of whom (71.15) had peptic ulcer and 82 patients (80.4%) were with GIB. All patients had used NSAIDs for over six weeks.

**Conclusion:** Age 65 years and above, cardiovascular and cerebrovascular diseases, antiplatelet drugs, DM, long-term use of NSAIDs, and corticosteroids are risk factors for the gastrointestinal complications associated with NSAIDs use. Family history of gastrointestinal bleeding, past history of peptic ulcers, and smoking are also risk factors. In our study, these findings were not statistically significant.

**Keywords:** risk factors, gastrointestinal bleeding, peptic ulcer, NSAID

## INTRODUCTION

NSAIDs (nonsteroidal anti-inflammatory drugs) are a broad class of non-glucocorticoid drugs used in anti-inflammatory, analgesic, and antipyretic therapies. Nonsteroidal anti-inflammatory drugs are among the most popular drugs, and their beneficial therapeutic properties are further documented to protect against various critical disorders, including cancer and heart attacks (1). NSAIDs are unfortunately associated with several serious complications that make different organs vulnerable to damage. However, NSAIDs may induce many side effects in the gastrointestinal tract, and the injury of gastric and duodenal mucosa provoked by NSAIDs has been widely studied (2). The significant risk factors for NSAID-related gastrointestinal complications are older age (age  $\geq 65$  years, especially  $\geq 70$  years); history of uncomplicated or complicated ulcer; concomitant use of other drugs, Diabetes mellitus, aspirin or other non-aspirin antiplatelet agents, anticoagulants, corticosteroids or alcohol and tobacco use; and *Helicobacter pylori* infection (3).

**Table 1.** Risk factors of NSAID related to the gastrointestinal complications

Age $\geq 65$ years (especially $>70$ years)
Administration of two or more NSAIDs at the same time
Attending therapy with aspirin and corticosteroids
<i>Helicobacter pylori</i> infection
Diabetes Mellitus
Alcohol and Smoking

## Co-administration of medications

Studies have evaluated the prevalence of NSAIDs and aspirin use to be 24.7% in the elderly (4). NSAIDs can cause injury anywhere in the GI tract, although the upper GI tract seems most vulnerable. Injuries can be divided into gastroduodenal, small bowel, and colonic.

About half of the patients who regularly take NSAIDs have gastric erosions, and 15% to 30% have ulcers that are noticed by endoscopic procedures. Clinical upper GI events (perforations, obstructions, bleeding, and uncomplicated ulcers) may occur in 3% to 4.5% of patients taking NSAIDs yearly and serious, complex events (perforation, obstruction, or significant bleeding) develop in approximately 1.5% of cases (5).

Several authors have reported that patients treated with NSAIDs had an estimated relative risk associated with current corticosteroid use. Hence, the combined use of corticosteroids and NSAIDs can lead to gastric ulcers (6).

The risk of bleeding with anticoagulants is probably caused by bleeding from clinically silent lesions caused by *Helicobacter pylori* or previous history of peptic ulcer. When conjoined with NSAID, the evaluated relative risk (RR) for expanding peptic ulcer disease rises to 4.4 compared to using steroids independently. The risk of developing peptic ulcer disease is notably lower with low-dose aspirin (81 mg) than full-dose aspirin (325 mg) (7). The RR of low-dose aspirin has been indicated to be 2.07 compared with full-dose for major gastrointestinal bleeding.

When low-dose aspirin is used with an NSAID, there is an additive increased risk of bleeding in patients developing a gastroduodenal ulcer (8,9). Nonsteroidal anti-inflammatory drug use in elderly patients with diabetes was associated with a higher risk of upper gastrointestinal bleeding (10). Diabetic patients are likewise inclined to have complicated peptic ulcer disease (PUD) like a peptic ulcer bleeding (PUB) probably because they were initially asymptomatic or have equivocal symptoms because of diabetic autonomic neuropathy. NSAID/aspirin use, Helicobacter pylori infection, history of ulcer/ulcer bleeding are all critical risk factors for PUB. This shows that older peptic ulcer history and NSAIDs are important risk factors for PUB in type II diabetic patients (11, 12).

Our study aimed to know more about the risk factors associated with gastrointestinal complications caused by NSAIDs in the elderly population in Albania.

### MATERIAL AND METHODS

We have retrospectively evaluated the medical files of patients hospitalized at the General Surgery Service, University Hospital Center “Mother Theresa” Tirana, Albania with the diagnosis gastrointestinal bleeding (GIB) or peptic ulcer. The medical records belonged to a ten years’ period, from 2011 until 2021.

We identified 307 patients hospitalized with these diagnoses, users of NSAID or corticosteroids to treat rheumatic pathologies. We considered age, gender, family and personal medical history of

peptic ulcer, concomitant diseases, other medications used, and their duration for all patients.

### RESULTS

We identified 260 females (85.2%) and 45 males (14.8%), with a mean age of 68.4 years (+ 13.4). Ninety of the patients (29.5%) had used antiplatelet drugs as concomitant cardiovascular and cerebrovascular diseases, in which 37 patients (35.9%) was diagnosed with peptic ulcer and 53 patients (26.2%) was diagnosed with gastrointestinal hemorrhage ( $p = 0.05$ ).

Fifty-nine patients (19.3%) had used cortisone for rheumatic disease, in which 13 patients (12.6%) was diagnosed with peptic ulcer and 46 patients (22.8%) was diagnosed with gastrointestinal bleeding ( $p = 0.034$ ).

One hundred twenty-five patients (78.1%) were diagnosed with Diabetes Mellitus, 43 of whom (71.15) had peptic ulcer and 82 patients (80.4%) was diagnosed with gastrointestinal bleeding. All patients had used NSAIDs for over six weeks.

The tables below explain clearly the results that we have obtained.

- The total number of patients were 251, respectively:

Females 206 (85.2%)	Males 45 (14.8%)
---------------------	------------------

- Ninety patients (29.5%) administrated antiplatelet drugs which,

37 patients (12.6%) had peptic ulcer	53 patients (26.2%) had GIB ( $p=0.05$ )
--------------------------------------	--

- Fifty-nine patients (19.3%) had used cortisone for rheumatic disease which

13 patients (12.6%) had peptic ulcer	46 patients (22.8%) had GIB (p = 0.034).
---	---

- One hundred twenty-five patients (78.1%) were diagnosed with Diabetes Mellitus in which,

43 patients (71.15%) had peptic ulcer	82 patients (80.4%) had GIB
--	--------------------------------

## DISCUSSION

In elderly patients balancing the risk and benefits of medicine need extra attention from the caregiver, because symptoms are often subtle and side effects more frequent, with significant adverse events being always a concern. This tendency is particularly evident with nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants, and antiplatelet agents because one of the essential complications, such as gastrointestinal (GI) bleeding, can result in significant morbidity in this population. Considering the medical challenge that this age group has, it was in the focus of this investigation. Non-steroidal anti-inflammatory drugs, including low-dose aspirin, are the most commonly used medicines. They are associated with gastrointestinal mucosal injury. Before prescribing them, it is essential to evaluate the patient's gastrointestinal risk factors such as age and history of peptic ulcers. Patients at high risk may need co-prescription of other drugs to reduce the risk of peptic ulcers. A daily dose of a proton pump inhibitor is the most effective strategy to

reduce the risk of peptic ulcers caused by non-steroidal anti-inflammatory drugs (13). People worldwide consume non-steroidal anti-inflammatory drugs (NSAIDs) every day due to their analgesic, anti-inflammatory, and antipyretic effect (14). NSAIDs or aspirin can harm the entire digestive tract, from the esophagus to the rectum. However, NSAID-associated complications are six times more frequent in the upper gastrointestinal tract than in the lower (15). Generally, the risk is dose-dependent and is more significant with more than one anti-inflammatory drug taken simultaneously (16).

## CONCLUSION

Age over 65 years, cardiovascular and cerebrovascular diseases, antiplatelet drugs use, Diabetes Mellitus, long-term use of NSAIDs, and use of corticosteroids are risk factors for the gastrointestinal complications associated with NSAIDs use. A gastroduodenal peptic ulcer is the most frequent complication. An NSAID-related peptic ulcer is due to these drugs' local and systemic action in the gastric mucosa-associated with the loss of the defensive systems. The risk of the upper gastrointestinal tract, such as bleeding or perforation, increases with the use of oral steroids or low dose aspirin in co-administration with nonsteroidal anti-inflammatory drugs.

**Acknowledgements:** None declared.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

## REFERENCES

1. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *BiochemPharmacol.* 2020;180:114147. doi:10.1016/j.bcp.2020.114147
2. Chinese Rheumatism Data Center; Chinese Systemic Lupus Erythematosus Treatment and Research Group. [Recommendation for the prevention and treatment of non-steroidal anti-inflammatory drug-induced gastrointestinal ulcers and its complications]. *ZhonghuaNeiKeZaZhi.* 2017 Jan 1;56(1):81-85. Chinese. doi: 10.3760/cma.j.issn.0578-1426.2017.01.021. PMID: 28056333.
3. Sostres C, Gargallo CJ, Arroyo MT, Lanás A: Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. *Best Pract Res ClinGastroenterol.* 2010, 24: 121-132.
4. Pilotto A, Franceschi M, Leandro G, et al. NSAID and aspirin use by the elderly in general practice: effect on gastrointestinal symptoms and therapies. *Drugs Aging* 2003;20(9):701–10.
5. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120(3):594–606.
6. Tsujimoto S, Mokuda S, Matoba K, et al. The prevalence of endoscopic gastric mucosal damage in patients with rheumatoid arthritis. *PLoS One.* 2018;13(7):e0200023. Published 2018 Jul 9. doi:10.1371/journal.pone.0200023
7. McQuaid KR. Systematic review and meta-analysis of adverse events of lowdose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; 119(8):624–38.
8. Kawasaki K. Low-dose aspirin and non-steroidal anti-inflammatory drugs increase the risk of bleeding in patients with gastroduodenal ulcer. *Dig Dis Sci* 2015;60(4):1010–5.
9. Lanás A. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol* 2015;13(5):906–12.e2.
10. Kim J, Lee J, Shin CM, Lee DH, Park BJ. Risk of gastrointestinal bleeding and cardiovascular events due to NSAIDs in the diabetic elderly population. *BMJ Open Diabetes Res Care.* 2015 Dec 18;3(1):e000133. doi: 10.1136/bmjdr-2015-000133. PMID: 26719806; PMCID: PMC4691662.
11. Luo JC, Lin HY, Lu CL et al. Dexamethasone inhibits basic fibroblast growth factor-stimulated gastric epithelial cell proliferation. *Biochem. Pharmacol.* 2008; 76: 841–9.
12. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet* 2002; 359: 14–22.
13. Drini M. Peptic Aust Prescr. 2017;40(3):91-93.

doi:10.18773/austprescr.2017.037 ulcer disease and non-steroidal anti-inflammatory drugs.

14. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. *Arthritis, Rheumatism, and Aging Medical Information System. Am J Ther*, 7(2), 115-121 (2000).

15. Lanas A, Perez-Aisa MA, Feu F et al. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with nonsteroidal antiinflammatory drug use. *Am J Gastroenterol*, 100(8), 1685-1693 (2005).

16. Garcia Rodríguez LA, Hernández-Díaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. *Arthritis Res.* 2001;3(2):98-101. doi:10.1186/ar146