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# Long-term aspirin use in patients hospitalized with ischemic colitis

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## Abstract

**Background** Ischemic colitis is a form of mesenteric ischemia that often presents in patients with vascular disease. Long-term aspirin use has been shown to improve the outcomes in patients with cardiovascular or cerebrovascular disease. However, the relationship between aspirin use and ischemic colitis is unclear.

**Methods** Patients with a diagnosis of ischemic colitis were identified using the 2020 Nationwide Inpatient Sample. Patients were stratified by long-term aspirin use at the time of hospitalization. Data were collected regarding mortality, bowel perforation, peritonitis, shock, blood transfusion, length of stay in days (LOS), hospital charges, age, sex, race, primary insurance, median income, hospital region, hospital size, and comorbidities. The relationship between aspirin use and outcomes was analyzed using multivariate regression analysis.

**Results** A total of 67,685 patients were included. Aspirin users had a mean age of 72.8 years compared to 66.8 years for non-aspirin users. Long-term aspirin use was associated with a lower risk of in-hospital mortality (P<0.001), bowel perforation (P<0.001), peritonitis (P=0.01), shock (P<0.001), and blood transfusion (P<0.001). The mean LOS was 6.1 days in the aspirin group compared to 9.4 days in the non-aspirin group. Ischemic colitis patients taking aspirin had a mean hospitalization charge of $87,123 compared to $161,610 for those not using aspirin.

**Conclusions** Our study examined the impact of aspirin use in ischemic colitis patients. Among patients hospitalized with ischemic colitis, we found that long-term aspirin use was associated with a lower risk of in-hospital mortality and adverse events.

**Keywords** Aspirin, ischemic colitis, mesenteric ischemia

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## Introduction

Ischemic colitis is the most common presentation of mesenteric ischemia, and was first described by Boley *et al* in 1963 [1]. It is a result of decreased blood supply in the setting of vascular disease and/or hypotension, and most often affects watershed areas with limited collateral flow, such as the splenic flexure and sigmoid colon. The rectum is often spared, as it has an alternate vascular supply [2]. Ischemic colitis is known to have a high in-hospital mortality rate, with studies estimating mortality at 11-29% [3-5]. Complications of ischemic colitis include bowel perforation, persistent hemorrhage, peritonitis and stricture formation [6]. The majority of patients are managed conservatively, though more severe cases may require surgical intervention [3]. Ischemic colitis is often associated with various risk factors, such as advanced age, atherosclerotic disease and coagulation disorders, making it a complex and multifaceted condition to manage [7].

Aspirin is a non-steroidal anti-inflammatory drug that has inhibitory effects on cyclooxygenases. Cyclooxygenases

have vasoconstrictive and anti-natriuretic effects, mediated by prostaglandin E-2 and prostacyclin synthesis; this helps lead to the vasodilatory and anti-platelet effects for which aspirin is mainly used [8]. Aspirin has been shown to provide a mortality benefit in patients with risk factors for cardiovascular disease [9]. However, its impact on gastrointestinal (GI) health, especially in the context of ischemic colitis, remains an area of ongoing investigation.

## Materials and methods

### Data source

The data used for this study were obtained from the Nationwide Inpatient Sample (NIS), the largest database of inpatient hospital admissions in the United States [10]. The Healthcare Cost and Utilization Project maintains and operates NIS as a 20% stratified sample of hospitalizations nationwide. The NIS is a reliable and valid method of obtaining hospitalization data, including outcomes. All patient information for each hospitalization is de-identified; therefore, Institutional Review Board approval was not required for this study.

### Ethical compliance with human/animal study

This study was performed in compliance with the Helsinki declaration regarding research involving human subjects.

### Study population

NIS was queried using the Internal Classification of Diseases 10$^{th}$ Version, Clinical Modification (ICD-10 CM) codes for patients hospitalized with a diagnosis of ischemic colitis. A total of 69,340 patients were identified during 2020. Of this group, 1655 lacked mortality or demographic information and were excluded from the study. Thus, a total of 67,685 patients were included. Patients were then stratified into 2 groups based on the presence or absence of long-term aspirin use at the time of hospitalization. The inclusion process for the study is outlined in Fig. 1.

### Study outcomes and variables

The primary study outcome was the effect of long-term aspirin use on in-hospital mortality in patients hospitalized with ischemic colitis. Secondary outcomes included bowel perforation, peritonitis, shock, blood transfusion, mean length of stay (LOS) and total hospitalization charges. The following definitions were used.

- Mortality: death during hospitalization.
- Bowel perforation: non-traumatic perforation of the large intestine.

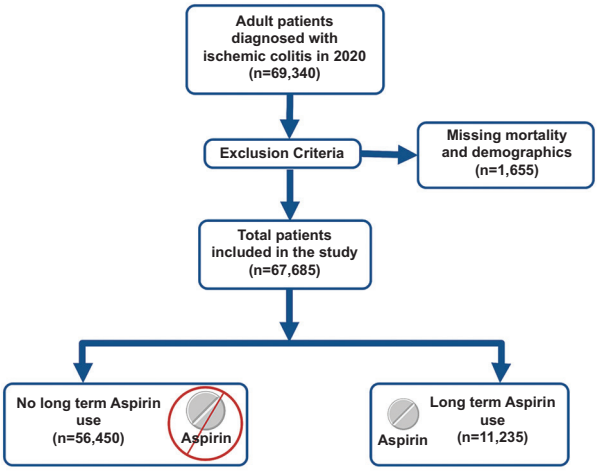


**Figure 1** Inclusion process for the study

- Peritonitis: inflammation of the peritoneum due to either bacterial causes via the bloodstream, or from organ rupture.
- Shock: hypotension with evidence of end-organ damage.
- Blood transfusion: administration of packed red blood cells during hospitalization because of anemia or acute blood loss.
- LOS: total number of days from admission to discharge.
- Hospitalization charges: cost billed to the primary expected payer for services rendered from admission to discharge.

Our primary exposure variable was long-term aspirin use. Other variables included in our analysis were age category (<44 years; 45-64 years; and >65 years), sex, race, primary insurance, median income, hospital region, hospital size, coronary artery disease, peripheral vascular disease, coagulation disorders, and presence of COVID-19 infection. The Charlson Comorbidity Index was used to assess comorbidities, and to predict mortality and resource use based on ICD-10 CM codes.

### Statistical analysis

NIS provides hospital-level discharge weights, which were used to create nationwide estimations. Continuous variables were compared using an independent samples *t*-test. Categorical variables were compared using the chi-square test. Univariate logistic regression was performed to elucidate the association between our variables and outcomes. We then performed multivariate regression analysis, while adjusting for variables with P<0.1 on univariate analysis. The adjusted odds ratio (aOR) was obtained with a 95% confidence interval (CI). A type I error of <0.05 was considered statistically significant. Data analysis was performed using STATA 18.0 (Texas).

## Results

### Patient characteristics

Of the 67,685 patients included in the study, 11,235 (16.6%) were documented as long-term aspirin users, while 56,450 (83.4%) were not. The majority of patients in the aspirin group were >65 years (76.4%), White (78.6%), had Medicare insurance (78.5%), and 3 or more comorbidities (59.2%). Complete baseline demographic information of the patients included in our study is outlined in Table 1.

### Outcomes

Confounders controlled for were variables that had P<0.1 on univariate analysis and included age category, sex, income, Charlson comorbidities, hospital size, and COVID-19 infection. Total in-hospital mortality was 12,840 (19%).

The mortality rate in the aspirin group was 11.9%, compared to 20.4% in the non-aspirin group (P<0.001). The risk of in-hospital mortality in patients with ischemic colitis was lower in the aspirin group, with an aOR of 0.52, 95%CI 0.45-0.60 (P<0.001) on multivariate analysis when controlling for confounders.

**Table 1** Patient characteristics

| Demographics | Aspirin use, total (percentage) | No aspirin use, total (percentage) | P-value |
|---|---|---|---|
| Age category | | | <0.001 |
| <44 years | 169 (1.5%) | 4968 (8.8%) | |
| 45-64 years | 2494 (22.2%) | 17,161 (30.4%) | |
| >65 years | 8584 (76.4%) | 34,378 (60.9%) | |
| Sex | | | 0.082 |
| Male | 4382 (39%) | 23,145 (41%) | |
| Female | 6853 (61%) | 33,305 (50%) | |
| Race | | | <0.001 |
| White | 8831 (78.6%) | 41,208 (73.1%) | |
| Black | 1157 (10.3%) | 7056 (12.5%) | |
| Hispanic | 753 (6.7%) | 4911 (8.7%) | |
| Asian/Pacific Islander | 2 (2.4%) | 1411 (2.5%) | |
| Native American | 35 (0.31%) | 288 (5.1%) | |
| Other | 191 (1.7%) | 1524 (2.7%) | |
| Primary expected payer | | | <0.001 |
| Medicare | 8819 (78.5%) | 36,918 (65.4%) | |
| Medicaid | 753 (6.7%) | 6548 (11.6%) | |
| Private | 1505 (13.4%) | 11,290 (20.1%) | |
| Uninsured | 157 (1.4%) | 1694 (3%) | |
| Median income (total household annual income) | | | 0.264 |
| Lowest quartile (poorest) | 2955 (26.3%) | 15,693 (27.8%) | |
| Second quartile | 3269 (29.1%) | 15,354 (27.2%) | |
| Third quartile | 2753 (24.5%) | 13,661 (24.2%) | |
| Highest quartile (wealthiest) | 2258 (20.1%) | 11,742 (20.8%) | |
| Hospital region | | | <0.001 |
| Northeast | 1708 (15.2%) | 11,234 (19.9%) | |
| Midwest | 3168 (28.2%) | 12,871 (22.8%) | |
| South | 4280 (38.1%) | 21,056 (37.3%) | |
| West | 2090 (18.6%) | 11,290 (20%) | |
| Hospital size | | | 0.046 |
| Small | 2562 (22.8%) | 11,459 (20.3%) | |
| Medium | 3247 (28.9%) | 16,427 (29.1%) | |
| Large | 5426 (48.3%) | 28,563 (50.6%) | |
| Charlson comorbidity index | | | |
| 0 | 90 (0.83%) | 1468 (2.6%) | <0.001 |
| 1 | 2089 (18.6%) | 12,588 (22.3%) | |
| 2 | 2404 (21.4%) | 10,895 (19.3%) | |
| 3 or more | 6651 (59.2%) | 31,556 (55.9%) | |
| Coronary artery disease | 5045 (44.9%) | 12,137 (21.5%) | <0.001 |
| Peripheral vascular disease | 1618 (14.4%) | 4742 (8.4%) | <0.001 |
| Coagulation disorder | 595 (5.3%) | 6943 (12.3%) | <0.001 |

A total of 3249 (4.8%) patients developed bowel perforation during hospitalization. The perforation rate was 2.7% in the aspirin group, compared to 5.3% in the non-aspirin group (P<0.001). Aspirin use was associated with a lower risk of bowel perforation, with an aOR of 0.51, 95%CI 0.38-0.66 (P<0.001) when adjusting for confounders on multivariate analysis.

A total of 745 patients developed peritonitis (1.1%). Peritonitis occurred in 0.6% of patients on aspirin, compared to 1.2% of patients not on aspirin (P=0.007). Aspirin was associated with a lower risk of peritonitis during hospitalization, with an aOR of 0.47, 95%CI 0.26-0.83 (P=0.01) on multivariate analysis.

A total of 5144 patients in our study population developed shock (7.6%). The incidence of shock was 5.4% in the aspirin group, compared to 8.1% in the non-aspirin group (P<0.001). Aspirin use was associated with a lower risk of shock, with an aOR of 0.69, 95%CI 0.57-0.85 (P<0.001) on multivariate analysis.

Blood transfusion was required in a total of 7648 patients (11.3%). Approximately 8.7% of patients in the aspirin group required blood transfusion, compared to 11.8% in the non-aspirin group (P<0.001). On multivariate analysis, aspirin use was associated with a lower risk for requiring blood transfusion during hospitalization, with an aOR of 0.72, 95%CI 0.62-0.85 (P<0.001).

The mean LOS was 6.1 days in the aspirin group, compared to 9.4 days in the non-aspirin group. Ischemic colitis patients with long-term aspirin use had a mean hospitalization charge of $87,123 compared to $161,610 in those without aspirin use. These outcomes are presented in Table 2.

## Discussion

In our study, we found a statistically significant difference in the mortality rate of ischemic colitis patients between aspirin users and non-aspirin users. This finding suggests that chronic aspirin use might confer a protective effect against in-hospital mortality in patients with ischemic colitis. The aOR on multivariate analysis, accounting for potential confounders, further supports the association between aspirin use and reduced mortality risk. Our study also assessed the occurrence of bowel perforation and peritonitis among patients hospitalized with ischemic colitis. The results indicated a lower incidence of bowel perforation in the aspirin group compared to the non-aspirin group. Similarly, the risk of peritonitis was lower in the aspirin group compared to the non-aspirin group. These findings are particularly relevant, as bowel perforation and peritonitis are severe complications that can significantly impact patient outcomes in ischemic colitis. Our study also found lower odds of shock and blood transfusion requirements among aspirin users. Additionally, aspirin use was associated with less resource utilization, with a shorter mean LOS and lower total hospitalization charges.

Though aspirin has been thought to directly damage GI mucosa and has been associated with increased risk of ulceration in ischemic colitis patients, studies have shown mixed results [11]. A retrospective study of 244 patients by Xiao *et al* found that long-term aspirin use may be associated with a more severe presentation of ischemic colitis, including a higher incidence of ulceration [12]. Additionally, a meta-analysis by Yuhara *et al* found that aspirin is associated with an increased risk of colonic diverticular bleeding [13]. This is in contrast to our study, which found more severe outcomes of ischemic colitis among patients who were not on aspirin compared to aspirin users. A retrospective study by Souk *et al* compared patients with non-variceal upper GI bleeding taking long-term aspirin for primary prophylaxis to those not on aspirin, and found a lower risk of mortality (aOR 0.15, 95%CI 0.03-0.64; P=0.002) in the aspirin group [14]. This study also found that total composite outcome was lower in the aspirin group compared to the non-aspirin group, at 10.6% vs 24.0% respectively (P=0.01). Composite outcome was defined as mortality, severe bleeding, re-bleeding, need for surgery or embolization. Severe hemorrhage was defined as blood pressure <90 mmHg, heart rate >120 beats/min, hemoglobin <7 g/dL on presentation, or transfusion of >3 units of blood during hospitalization [14].

**Table 2** Outcomes on multivariate regression analysis

| Outcomes | Percentage among aspirin users | Percentage among non-aspirin users | Adjusted odds ratio among aspirin users | 95% confidence interval | P-value |
|---|---|---|---|---|---|
| Death during hospitalization | 11.9% | 20.4% | 0.52 | 0.45-0.60 | <0.001 |
| Bowel perforation | 2.7% | 5.3% | 0.51 | 0.38-0.66 | <0.001 |
| Peritonitis | 0.6% | 1.2% | 0.47 | 0.26-0.83 | 0.01 |
| Shock | 5.4% | 8.1% | 0.69 | 0.57-0.85 | <0.001 |
| Blood transfusion | 8.7% | 11.8% | 0.72 | 0.62-0.85 | <0.001 |
| | Long-term aspirin use | 95% confidence interval | No long-term aspirin use | 95% confidence interval | |
| Length of stay (days) | 6.1 days (mean) | 5.8-6.5 days | 9.4 days (mean) | 9.1-9.7 days | |
| Total charges | $87,123 (mean) | $80,590 - $93,655 | $161,610 (mean) | $152,936 - $170,283 | |

A retrospective cohort study by Ahsberg *et al* included 766 patients with upper GI bleeding due to peptic ulcer disease, and found that patients using aspirin upon presentation had a significantly lower risk of fatal outcome (aOR 0.12, 95%CI 0.012-0.67; P=0.032) [15]. These findings are consistent with our study, which also found lower odds of mortality, shock and blood transfusion among aspirin users, suggesting that the benefits of aspirin might not be limited solely to the upper GI tract. Studies involving aspirin and lower GI pathology are limited; however, Patel *et al* found that aspirin use was not associated with a greater risk of being hospitalized among patients with inflammatory bowel disease [16]. This is consistent with our study, which found lower odds of peritonitis, bowel perforation and other adverse outcomes among aspirin users with ischemic colitis.

Though the mechanisms remain unclear, the protective effects of long-term aspirin use in patients with ischemic colitis may be similar to its effects in those with cardiovascular or cerebrovascular disease. The majority of the aspirin users in our study were >65 years old, with evidence of atherosclerotic disease, including coronary artery disease or peripheral vascular disease. Mesenteric ischemia is most commonly associated with atherosclerosis, and patients often have evidence of peripheral vascular disease at other sites [17]. Most cases of ischemic colitis are non-occlusive in nature, and involve a decrease in blood pressure with preexisting atherosclerotic plaques in the mesenteric vasculature [18]. Peripheral vasodilation in patients with atherosclerosis is modulated by vasoconstrictors released from the endothelium in response to cyclooxygenases. By inhibiting this process, aspirin is thought to inhibit atherosclerosis progression, endothelial dysfunction, thrombosis, and vasoconstriction [19]. The beneficial effects of aspirin in ischemic colitis may be related to these pathophysiological effects noted in the vasculature of other organ systems.

Our study had several limitations. Given the features of the NIS data used in the study, hospital readmissions cannot be tracked, and each subject is viewed as a single hospitalization without knowledge of whether a patient was readmitted. The cause of death is not documented, making the ultimate mortality causes unclear. Additionally, documentation of diagnoses in the US for in-hospital visits are documented using ICD-10 codes, which may lead to coding errors in the form of incorrect input. Further limitations include the inability to differentiate between occlusive and non-occlusive ischemic colitis, or to identify patients taking other oral antithrombotic therapy, due to the nature of ICD-10 codes. Medication dosing is not available through the NIS, and therefore we were unable to determine the aspirin dosing and the indication as primary or secondary prophylaxis. Additionally, we were unable to differentiate whether shock was a complication of ischemic colitis, or if it was the inciting factor that caused the ischemia. We believe that our study's strengths are its large population size and lack of regional bias, which can help mitigate the above limitations. A large amount of data exists in the literature regarding the possible benefits and risks of long-term aspirin use in a myriad of conditions and disease states, and further studies are needed regarding its use in patients with ischemic colitis. Our study findings suggest that aspirin may have a benefit in patients with ischemic colitis. Further studies are needed to assess this relationship in greater detail.

**Summary Box**

**What is already known:**

- Ischemic colitis is associated with significant morbidity and mortality
- Ischemic colitis is mostly seen in patients with risk factors for cardiovascular disease
- Long-term aspirin use has a mortality benefit in patients with vascular disease, and some studies have also shown protective effects in other disease states

**What the new findings are:**

- Long-term aspirin use is associated with a lower risk of in-hospital mortality in patients with ischemic colitis
- Long-term aspirin use is associated with a lower risk of complications of ischemic colitis including peritonitis, bowel perforation, shock, and need for blood transfusion
- Long-term aspirin use may reduce resource utilization in patients hospitalized with ischemic colitis

## References


1. Boley SJ, Schwartz S, Lash J, Sternhill V. Reversible vascular occlusion of the colon. *Surg Gynecol Obstet* 1963;**116**:53-60.
2. Theodoropoulou A, Koutroubakis IE. Ischemic colitis: clinical practice in diagnosis and treatment. *World J Gastroenterol* 2008;**14**:7302-7308.
3. Gilshtein H, Hallon K, Kluger Y. Ischemic colitis caused increased early and delayed mortality. *World J Emerg Surg* 2018;**13**:31.
4. Yadav S, Dave M, Edakkanambeth Varayil J, et al. A population-based study of incidence, risk factors, clinical spectrum, and outcomes of ischemic colitis. *Clin Gastroenterol Hepatol* 2015;**13**:731-738.e1-e6.
5. O'Neill S, Yalamarthi S. Systematic review of the management of ischemic colitis. *Colorectal Dis* 2012;**14**:e751-e763.
6. Netz U, Galandiuk S. The management of ischemic colitis. Current surgical therapy. 12th edition, Elsevier, Philadelphia, 2017, pp. 171-176.
7. Cubiella Fernández J, Núñez Calvo L, González Vázquez E, et al. Risk factors associated with the development of ischemic colitis. *World J Gastroenterol* 2010;**16**:4564-4569.
8. Messerli FH. Aspirin: a novel antihypertensive drug? Or two birds with one stone? *J Am Coll Cardiol* 2005;**46**:984-985.
9. Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *Am J Med* 2011;**124**:621-629.
10. Healthcare Cost and Utilization Project (HCUP) Content last reviewed October 2022. Agency for Healthcare Research and Quality, Rockville, MD. Available from: https://www.ahrq.gov/data/hcup/index.html [Accessed 14 November 2023].
11. Martínez M JD, Molano V JC, Henao R SC. Gastroduodenal mucosal injuries by aspirine. Management of the risks. *Rev*

*Gastroenterol Peru* 2016;**36**:129-134.
12. Xiao W, Zhou SY, Wu K, et al. Low-dose aspirin and the severity of ischemic colitis: A single-center retrospective study. *Turk J Gastroenterol* 2020;**31**:848-852.
13. Yuhara H, Corley DA, Nakahara F, et al. Aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. *J Gastroenterol* 2014;**49**:992-1000.
14. Souk KM, Tamim HM, Abu Daya HA, Rockey DC, Barada KA. Aspirin use for primary prophylaxis: Adverse outcomes in non-variceal upper gastrointestinal bleeding. *World J Gastrointest Surg* 2016;**8**:501-507.
15. Åhsberg K, Höglund P, Staël von Holstein C. Mortality from peptic ulcer bleeding: the impact of comorbidity and the use of drugs that promote bleeding. *Aliment Pharmacol Ther* 2010;**32**:801-810.
16. Patel P, Gao G, Gulotta G, et al. Daily aspirin use does not impact clinical outcomes in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2021;**27**:236-241.
17. Sardar P, White CJ. Chronic mesenteric ischemia: diagnosis and management. *Prog Cardiovasc Dis* 2021;**65**:71-75.
18. Misiakos EP, Tsapralis D, Karatzas T, et al. Advents in the diagnosis and management of ischemic colitis. *Front Surg* 2017;**4**:47.
19. Vanhoutte PM, Shimokawa H, Feletou M, Tang EH. Endothelial dysfunction and vascular disease—a 30th anniversary update. *Acta Physiol (Oxf)* 2017;**219**:22-96.