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Factors associated with diverticular bleeding and re-bleeding: A United States hospital study

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ABSTRACT

OBJECTIVE: Diverticular bleeding is the most common cause of lower gastrointestinal bleeding. Arteriovascular disease, metabolic syndromes, non-steroidal anti-inflammatory drugs (NSAIDs), anti-thrombotics, and anticoagulants have been suggested as risk factors. There is a paucity of studies addressing factors associated with diverticular re-bleeding, especially in the United States. The aim of this study is to evaluate factors associated with colonic diverticular bleeding and re-bleeding in a US community-based hospital.

METHODS: We conducted a retrospective, case-control study to analyze the factors associated with diverticular bleeding. Between January 2010 and July 2011, 93 patients were admitted to our hospital with a primary diagnosis of acute diverticular bleeding. We compared them to 152 patients who were admitted with a primary diagnosis of diverticulitis within the same period. We collected the data from the medical records of each patient in relation to the demographics, comorbidities, medications, social habits, location of diverticulosis, length of stay in hospital, and re-bleeding rate within two years of the first bleeding episode.

RESULTS: Cerebrovascular accident (p=0.009), coronary artery disease (p=0.037), diabetes mellitus (p=0.046), obstructive sleep apnea (p=0.033), NSAIDs (p=0.038), anti-thrombotics (p=0.001), anticoagulants (p=0.002), calcium channel blockers (p=0.009), and bilateral diverticulosis (p=0.001) were significantly associated with diverticular bleeding compared to diverticulitis. Recurrence of bleeding was noted in 26/93 (28%) of case group patients within 2 years of first bleeding episode (p=0.001). Bilateral colonic involvement, anti-coagulants and elderly age (≥65 year) were found as factors having closer relation to diverticular re-bleeding, although they did not reach statistical significance.

CONCLUSION: This study reveals that arteriovascular disease, diabetes mellitus, NSAIDs, anti-thrombotics, anti-coagulants, calcium channel blockers and sleep apnea are factors significantly associated with diverticular bleeding. It also shows that bilateral colonic involvement, elderly age and anti-coagulants have closer relation to diverticular re-bleeding. Prospective studies in patients with diverticular bleeding remain a need to shed more light on the causality of these factors to this prevalent condition.

Keywords: Bleeding; community; diverticula; diverticulum; factor; outcome.

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Diverticular disease accounts for 312,000 admissions and 1.5 million days of inpatient care annually in the United States, with costs of care exceeding 2.6 billion dollars.1 Diverticular disease of the gastrointestinal tract is more common in developed countries, and occurs more often in older individuals. Prevalence of diverticular disease increases to 50 to 66% in patients older than age 80 years [1], and is equally seen in both men and women [2]. Many patients diagnosed with diverticulosis remain asymptomatic; while approximately 10–20% go on to develop symptoms such as diverticular hemorrhage [3] Although the patients with diverticulosis usually remain asymptomatic, symptomatic patients suffer from various symptoms ranging from irritable bowel syndrome (IBS)-type symptoms to disabling recurrent abdominal pain [4]. Diverticular hemorrhage can become severe with substantial morbidity as well as a mortality rate of 10% to 20% [5].

Diverticular bleeding pathogenesis is not completely understood, and one common theory is that it originates from repetitive injury overtime to the vasa recta from musculature contraction. Approximately 70 to 80% of diverticular bleedings will resolve spontaneously, with re-bleeding occurring in up to 38% of patients [6]. Patients with uncomplicated diverticulitis generally respond well to outpatient, conservative treatment, such as oral antibiotics. However, surgical treatment may be required for recurrent cases, those with recurrent diverticular bleeding, and for diverticulitis complicated by large abscess formation, perforation, intestinal obstruction, or fistula formation [7].

While there have been some studies assessing factors associated with diverticular hemorrhage; there is a paucity of studies evaluating the factors associated with diverticulitis, diverticular bleeding, and diverticular re-bleeding, most notably in the United States. Factors that have been postulated to be associated with an increased risk for diverticular bleeding include arteriovascular disease, metabolic syndrome, non-steroidal anti-inflammatory drugs (NSAIDS), anti-thrombotics, and anti-coagulants. NSAIDs and aspirin have been identified in studies to increase risk for acute lower gastrointestinal bleeding, including acute diverticular bleeding as well as re-bleeding. Other factors associated with diverticular bleeding that have been mentioned in the literature include a large number of diverticula, hypertension, and arteriosclerotic diseases including ischemic heart disease and chronic renal failure [8]. Patients with chronic kidney disease have been noted to have radiologic findings consistent with diverticular disease, yet present without symptoms [9]. Calcium channel blockers have also been suggested as a factor associated with higher incidence of diverticular bleeding [10].

The purpose of this study was to evaluate the factors associated with colonic diverticular bleeding and re-bleeding, defined as a hospital admission within two years of a previous diverticular bleeding, in a United States hospital.

MATERIALS AND METHODS

In this study, we utilized a case-control approach to analyze factors associated with diverticular bleeding and re-bleeding. Between January 2010 and July 2011. 93 patients were admitted to our hospital with primary diagnosis of acute diverticular bleeding based on clinical presentation, colonoscopic and radiographic examination during hospital stay.

Diverticular bleeding was defined as lower gastrointestinal bleeding manifested by painless hematochezia in presence of active bleeding or stigmata of bleeding from affected diverticula during colonoscopic exam without presence of other identifiable bleeding source. In order to analyze factors associated with diverticular hemorrhage, a control group consisting of 152 patients, all of whom were admitted within the same time period with primary diagnosis of acute diverticulitis based on clinical presentation and radiologic evidence of diverticulitis on computed tomography, were used. We used diverticulitis as a control group since this condition is one of the major complications of diverticular disease and the patient may require admission. The medical records of each patient in both the case and control groups were screened for information regarding demographics, comorbidities, medications, findings of colonoscopy, location of diverticulosis, outcome of admission, complications including surgical intervention, hemoglobin level at time of presentation, and re-bleeding rate within two years of the first bleeding episode. We excluded patients who were pregnant, patients who had a concomitant severe active medical illnesses including sepsis, myocardial infarction, stroke, patients with end-stage renal disease, terminal cancer, or those patients who were admitted for other medical or surgical reasons and then developed gastrointestinal bleeding during their admission. Inform consent was obtained from all participants. This study was approved by each institutional review board involved in the study.

Table 1. Demographics and characteristics of patients, and comparison of different variables between diverticulosis and diverticulitis groups

	Diverticulosis (case group)	Diverticulitis (control group)	p
Age (years), mean±SD	73.3±12.1	59.2±13.1	<0.001
Gender (M/F)	1.4:1	1.8:1	0.37
Race (W/B)	1:1	1.7:1	0.035*
Length of stay (days)	5.85±1.41	6.11±0.71	>0.05
Hemoglobin level at admission (g/dL), mean±SD	10.2±2.46	12.6±2.0	<0.001
BMI, mean±SD	32.2±5.0	31.2±10.8	0.068
Hypertension, %	74.1	75	0.88
Cerebrovascular accident, %	13.9	4.6	0.009
Coronary artery disease, %	32.2	20.3	0.04
Diabetes mellitus, %	35.4	23.6	0.046
Chronic kidney disease, %	23.6	15.7	0.12
Obstructive sleep apnea, %	7.5	1.9	0.03
Gout, %	11.8	8.5	0.40
Alcohol use, %	12.9	7.2	0.14
Smoking, %	15	18.4	0.49
NSAIDs use, %	18.2	9.2	0.03
Aspirin/anti-thrombotics, %	48.3	23.6	0.001
Warfarin/anticoagulants, %	15.0	2.6	0.002
Proton pump inhibitor, %	25.8	32.2	0.28
ACEI/ ARB, %	49.4	49.3	0.98
Beta blocker, %	46.2	34.2	0.06
Calcium channel blockers, %	37.6	22.3	0.01

*Was more significant in Black patients. BMI: Body mass index; NSAIDs: Non-steroidal anti-inflammatory drugs; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

Statistical analysis

Descriptive methods with use of mean and standard deviation were utilized. To examine the differences in the distribution among case and control groups we used Student's t-test, Pearson Chi-Square or Fischer's Exact Test, when appropriate. Logistic regression analysis was used to examine the interaction between different factors. Alpha level of significance was set at <0.05.

RESULTS

Forty-three (46%) patients included in the case group had diverticular disease in the left colon, 5 (5%) in the right, and 37 (40%) presented with bilateral diverticular disease. Eight patients (9%) did not have a colonoscopy for various reasons, including advanced age. 94% of the control group had diverticular disease in the left colon. The mean age for case and control groups was 73.3±12.1, vs. 59.2±13.1 years, respectively. There was no significant difference between the two groups in regards to gender, body mass index (32.2±5.0 vs. 31.2±10.8) or length of stay (5.85±1.41 days vs. 6.11±0.71 days). African American patients were found to have more association with diverticular bleeding when compared to diverticulitis (white: black ratio 1:1 vs. 1.7:1, p=0.035 for diverticular bleeding vs. diverticulitis).

Table 1 shows the demographics and characteristics of patients, and comparison of different variables between case and control groups.

Hypertension was not found to have significant association with either diverticular bleeding or re-bleeding, whereas cerebrovascular accident (CVA) was found to be significantly associated with diverticular bleeding (p=0.009) but not for re-bleeding. This pattern of association with diverticular bleeding but not re-bleeding was also seen with coronary artery disease (CAD)

(p=0.037), diabetes mellitus (p=0.046), obstructive sleep apnea (OSA) (p=0.033). Chronic kidney disease (CKD) (defined as GFR <60 ml/min/1.73 m^2 for >3 months) was not shown to be significantly associated with diverticular bleeding or re-bleeding. Multiple logistic regression analysis showed no significant interaction between these variables to further increase risk of diverticular bleeding or re-bleeding.

Diverticular bleeding, but not re-bleeding, was shown to increase in patients who used NSAIDs or aspirin, as well as those who used calcium channel blockers (CCBs). In contrast, proton pump inhibitors (PPIs) showed no difference in relation to diverticular bleeding or re-bleeding. In patients taking both NSAIDs and a PPI, no interaction effect was seen with respect to increasing the risk of bleeding or re-bleeding. Anticoagulants such as Warfarin, as well as anti-thrombotic drugs such as Aspirin and Plavix, showed a higher association with diverticular bleeding; however, they did not reach the statistical significance for diverticular re-bleeding (p=0.11 for anticoagulant use and 0.5 for aspirin/anti-thrombotic use). Alcohol use (defined as >2 drinks/day for males and >1 drink for females) was not found to be significantly associated with either diverticular bleeding or re-bleeding when compared with diverticulitis group.

Gender showed no significant difference between the rates of bleeding and re-bleeding. Age was defined in our study into four groups: very elderly (≥80 year old), elderly (65–79), middle age (45–64), and young (≤44) patients. The older a patient, the higher the association with diverticular bleeding, where 27/35 (77%)of very elderly, 39/81 (48%) of elderly, 26/105 (25%) of middle age, and only 4% of young patients in the case group had developed diverticular hemorrhage. The very elderly patients were the closest of the four groups to being statistically significant for re-bleeding (p=0.08). Body mass index (BMI) was grouped as: normal (BMI 18–25), overweight (BMI 25–29.9), and obese (BMI ≥30), was not significantly different between the two groups for either bleeding or re-bleeding.

Left-sided bleeding occurred more commonly out of the three groups, and right-sided bleeding occurred least commonly. Bilateral diverticulosis was a factor that was significantly associated with diverticular bleeding (p=0.001). Recurrence of bleeding was noted in 26/93 (28%) of case group patients within 2 years of first bleeding episode (p=0.001).

While there are myriad of outcomes for patients presenting to the hospital with diverticular bleeding, death as an outcome was not shown to be more prevalent among those patients hospitalized with diverticular bleeding versus diverticulitis. The length of stay in the hospital and the risk for re-bleeding were independent of each other in this study; no significant correlation was found. Not unexpectedly, at the time of admission those patients presenting with a diverticular bleeding had significantly lower levels of hemoglobin than those with diverticulitis (p=<0.01).

DISCUSSION

Diverticular bleeding accounts for numerous hospitalizations throughout the world, yet few studies have identified specific factors leading to an increased risk of bleeding. Our study confirms that certain co-morbidities are more associated with diverticular-bleeding, including cardiovascular diseases (CVA, CAD) and diabetes mellitus. The association between OSA and diverticular hemorrhage is the first of its kind to be mentioned in the literature. Such an association could be explained by the higher prevalence of sleep apnea among patients with cardiovascular disease, who in turn have higher risk for diverticular hemorrhage. A previous study noted that apart from NSAIDs and anticoagulants, arterial hypertension had been shown to be an independent risk factor for colonic diverticular bleeding [11]. This alludes that arteriosclerosis and associated diseases such as metabolic syndrome could therefore play an important role in the pathogenesis of acute diverticular bleeding; yet, our study did not show that hypertension is associated with a higher risk for diverticular bleeding. The high prevalence of hypertension and metabolic syndrome in study population might be explaining this non-significant association.

In our study African American patients and the elderly were shown to have a higher association with diverticular bleeding, while gender, as previously stated in the literature, had no bearing on the risks of bleeding or re-bleeding. Although approximately 70 to 80% of diverticular bleeding will resolve spontaneously, re-bleeding occurs in up to 38% of patients, thus making it a pertinent factor to explore. In our study, we found very elderly age (≥80) to be an important factor for re-bleeding, close to reach statistical significance (p=0.08). Location of the bleeding was also examined and bilateral disease was a significant factor for diverticular bleeding, (bilateral 9/39, left/sigmoid 23/186, and right-sided disease

Table 2. Factors with close significance for diverticular re-bleeding

	p
Bilateral colonic involvement	0.10
Anti-coagulant use	0.11
Very elderly age (≥80)	0.08

Table 3. Outcome of admission, surgical intervention, complications, and re-bleeding rate

	Diverticulosis (case group) %	Diverticulitis (control group) %	p
Outcome (death)	3.2	1.3	0.3
Surgical intervention	5.3	26	<0.001*
Complications**	10.7	33.5	<0.001*
Re-bleeding within 2 years	27.9	7.2	0.001

*Was more significant in diverticulitis group. **Complications include abscess or fistula formation, intestinal obstruction, peritonitis, sepsis, perforation or need for colonic resection or laparotomy.

2/12 in both groups), bilateral involvement was close to reach statistical significance for diverticular re-bleeding (p=0.10). Table 2 shows factors with close significance for diverticular re-bleeding.

Table 3 reveals a staggering difference in rates of re-bleeding within 2 years between those patients with diverticulosis versus diverticulitis, with the former resulting in significantly more re-bleeding incidences (27.9% vs. 7.2%).

While the difference in death as an outcome between the two groups was shown to be insignificant, surgical intervention and complications (abscess or fistula formation, intestinal obstruction, peritonitis, sepsis, perforation or need for colonic resection or laparotomy) were higher in the diverticulitis group (p<0.001).

Our study verifies that certain medications including NSAIDs, ASA, Anti-coagulants, and CCBs are associated with a higher rate of diverticular hemorrhage. The strong association between diverticular bleeding and the use of NSAIDs as evaluated by our study agrees with the current literature; however, unlike a previous study on diverticular bleeding in Japan [12] our study showed no increased risk of NSAID use and diverticular re-bleeding. This was also true for aspirin and the risk of diverticular bleeding and re-bleeding. Anticoagulants such as Warfarin, as well as other anti-thrombotic drugs such as Clopidogrel, have been mentioned in the literature to increase the risk of diverticular bleeding, which our study's results concur with. Delving further into the effect of anti-coagulants on re-bleeding, no association was found between any of the drugs and diverticular re-bleeding. Proton pump inhibitor use exhibited no increased diverticular bleeding or re-bleeding risk among patients. Our study also verifies that calcium channel blockers are associated with diverticular bleeding, an observation that has been described in a European study, but up to this point had yet to reveal itself in a US based study.

This study used a retrospective case-control approach in order to identify factors associated with diverticular hemorrhage, as well as delineate the common and distinctive factors associated with diverticular bleeding and re-bleeding. The retrospective approach may have led to selection bias. To address that we had selected patients who were admitted with a primary diagnosis of diverticulitis (in contrary to other matching groups) as the control group since non-bleeding diverticulosis patients may not necessarily get admitted to the hospital. Other limitations include the possibility of the patients going to other facilities for their illness (diverticular bleeding or re-bleeding), which may have under estimated the prevalence of re-bleeding. Reviewing patients' population and demographics showed that majority of the patients had their medical care most of the time at our facility, as it is the main hospital in the region. Our findings may in fact have some overestimation due to higher prevalence of metabolic syndrome in the region of study.

Conclusion

This case-control study reveals that cardiovascular disease, diabetes mellitus, NSAIDs, anti-thrombotics, anti-coagulants, calcium channel blockers (CCBs) and obstructive sleep apnea (OSA) are significant risk factors associated with diverticular bleeding. It also suggests that bilateral colonic involvement increases the risk for diverticular bleeding. Bilateral involvement, anti-coagulant use and elderly age (≥65 year) were found as factors having closer relation to diverticular re-bleeding, although that did not reach statistical significance. This is the first study to introduce OSA as a possible risk factor associated with diverticular bleeding, which may have been

mediated by the high prevalence of cardiovascular disease and metabolic syndromes in the study population. Advanced age, especially in very elderly (≥80 year-old) had a strong association with diverticular bleeding. CCBs have been described in a German study as a risk factor associated with diverticular hemorrhage; our study confirms this observation in a United States hospital. Interestingly, obesity was not shown to be a significant risk factor for diverticular bleeding in our study. This may be due to the high prevalence of obesity in the region where the study was conducted.

As a significant contributor to hospital admissions, diverticular bleeding, and re-bleeding, risk factors are a prime target for investigation in order to prevent or decrease the number of hospital admissions, and to improve morbidity from the disease. Further investigation into causality of these risk factors for diverticular bleeding and re-bleeding needed to be explored in more prospectively designed studies.

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