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Evaluation Of Clinical Features And Risk Factors Affecting Bleeding In Patients With Gastrointestinal Angiodysplasia

Gastrointestinal Anjiyodisplazili Hastalarda Kanamayı Etkileyen Klinik Özellikler Ve Risk Faktörlerinin Değerlendirilmesi

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ABSTRACT

AIM:
The study aimed to evaluate the clinical features and risk factors affecting bleeding in patients with angiodysplasia.

MATERIAL AND METHOD:
This retrospective study was conducted between January 2016 and December 2019 and included patients who underwent endoscopy/colonoscopy examination for any reason at two institutions (n=2177). Patients with angiodysplasia were divided into two groups according to their bleeding status, and their clinical features and risk factors affecting bleeding were analyzed.

RESULTS:
Angiodysplasia was detected in 44 (2.02%) patients who underwent endoscopy and colonoscopy. Bleeding was detected in 25% (n=11) of patients with angiodysplasia. The frequency of anticoagulant use (p=0.016) and heart disease frequency (p=0.008) were higher in patients with angiodysplasia with bleeding. Hemoglobin (p=0.001), hematocrit ($p < 0.001$), platelet levels (p=0.009) and total iron binding capacity (p=0.036) were found to be significantly lower in patients with bleeding angiodysplasia. It was found that patients using anticoagulant had a 12.917-fold higher risk of bleeding than nonusers (OR:12.917, 95%CI: 2.014-82.830, p=0.007). Bleeding was not associated with age (p=0.196), gender (p=0.326), number of lesions (p=0.063), gastric lesion (p=0.880), duodenal lesion (p=0.472), colonic lesion (p=0.947), size of lesion (p=0.789), nonsteroidal anti-inflammatory drugs use (p=0.631), hypertension (p=0.163), cirrhosis (p=0.179), coronary artery disease (p=0.448) and heart diseases (p=0.207).

CONCLUSION:
The use of anticoagulant increases the risk of bleeding in patients with gastrointestinal angiodysplasia. Risk factors affecting bleeding in patients with gastrointestinal angiodysplasia need to be evaluated in comprehensive prospective studies.

Keywords:
Arteriovenous Malformations, Angiodysplasia, Endoscopy, Colonoscopy, Gastrointestinal Hemorrhage, Risk Factors

ÖZET

AMAÇ:
Bu çalışma, anjiyodisplazili hastalarda kanamayı etkileyen klinik özellikleri ve risk faktörlerini değerlendirmeyi amaçlamıştır.

GEREÇ VE YÖNTEM:
Bu retrospektif çalışma Ocak 2016 ile Aralık 2019 tarihleri arasında yapılmış olup, iki kurumda herhangi bir nedenle endoskopi/kolonoskopi tetkiki yapılan hastalar dahil edilmiştir. Anjiyodisplazili hastalar kanama durumlarına göre iki gruba ayrılarak klinik özellikleri ve kanamayı etkileyen risk faktörleri incelendi.

BULGULAR:
Endoskopi ve kolonoskopi yapılan 44 (%2,02) hastada anjiyodisplazi tespit edildi. Anjiyodisplazili hastaların %25'inde (n=11) kanama tespit edildi. Kanamalı anjiyodisplazi hastalarında antikoagülan kullanım sıklığı (p=0,016) ve kalp hastalığı sıklığı (p=0,008) daha yüksekti. Kanamalı anjiyodisplazi hastalarında hemoglobin (p=0,001), hematokrit ($p < 0,001$), trombosit düzeyleri (p=0,009) ve toplam demir bağlama kapasitesi (p=0,036) anlamlı olarak daha düşük bulundu. Antikoagülan kullanan hastaların, kullanmayanlara göre 12.917 kat daha yüksek kanama riskine sahip olduğu bulundu (OR:12,917, %95 GA: 2,014-82,830, p=0,007). Kanama yaş (p=0,196), cinsiyet (p=0,326), lezyon sayısı (p=0,063), mide lezyonu (p=0,880), duodenum lezyonu (p=0,472), kolon lezyonu (p=0,947), lezyon boyutu (p=0,789), nonsteroid antiinflamatuar ilaç kullanımı (p=0,631), hipertansiyon (p=0,163), siroz (p=0,179), koroner arter hastalığı (p=0,448) ve kalp hastalıkları (p=0.207) ile ilişkili değildi.

SONUÇ:
Antikoagülan kullanımı gastrointestinal anjiyodisplazili hastalarda kanama riskini artırmaktadır. Gastrointestinal anjiyodisplazili hastalarda kanamayı etkileyen risk faktörlerinin kapsamlı prospektif çalışmalarla değerlendirilmesi gerekmektedir.

Anahtar Kelimeler:
Arteriovenöz Malformasyonlar, Anjiyodisplazi, Endoskopi, Kolonoskopi, Gastrointestinal Kanama, Risk Faktörleri

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INTRODUCTION

Gastrointestinal angiodysplasias, also called angioectasias, are defined as vascular malformations consisting of abnormal, ectatic, enlarged and coiled arterial/venous capillaries, which are usually smaller than 5 mm and are located in the mucosal and submucosal layers of the gastrointestinal tract. 1,2 Affected vessels have a histological structure lined with endothelium with little or no smooth muscle.3

Because most are asymptomatic, gastrointestinal angiodysplasias (whose exact prevalence is unknown) present great difficulties in diagnosis and treatment due to their insidious disease behavior, inaccessibility of affected areas and limitations of current diagnostic procedures.2 However, such cases are increasingly identified today, probably due to improvements in endoscopic image resolution and increased recognition of angiodysplasias as important causes of gastrointestinal blood loss.3 Today, angiodysplasias are known to be frequently detected in the right colon and cecum, usually in patients older than 60 years of age and rarely before the age of 50 . About two-thirds of angiodysplasia cases occur in patients aged 70 years or older.4,5

The clinical effects of gastrointestinal angiodysplasias can range from being asymptomatic (incidental diagnosis) to life-threatening bleeding.6 Angiodysplasias are responsible for approximately 5% to 10% of all cases of gastrointestinal bleeding.2,7 The reason for elevated bleeding risk in patients with angiodysplasia has not been fully elucidated.8 Therefore, it is important to reveal risk factors related to these bleedings, which can be life-threatening in some cases, to be able to devise interventions for prevention and treatment.
This study aimed to evaluate the clinical features of gastrointestinal angiodysplasia cases according to the bleeding status, and to identify risk factors associated with bleeding.

MATERIAL AND METHOD

This retrospective study was carried out between January 2016 and December 2019, by evaluating the medical records of patients who underwent endoscopy/colonoscopy for any reason (anemia, gastrointestinal bleeding, inflammatory bowel disease, etc.) at two centers (Eskişehir City Hospital and Ministry of Health Yunusemre State Hospital).

The study protocol was approved by the Non-Invasive Clinical Research Ethics Committee of Eskisehir Osmangazi University (Decision no: 02, Decision date: 18.01.2022). The research was carried out in accordance with the Declaration of Helsinki.

Informed consent is obtained from all patients before colonoscopy in both institutions where research data were obtained. Due to the retrospective nature of the study, written or verbal consent was not obtained from the patients. Endoscopy/colonoscopy examinations were performed by specialist physicians. Within the scope of the study, data of 2177 patients were evaluated. It was found that 44 of the evaluated patients were diagnosed with angiodysplasia. Vascular malformations less than 5 mm in size, consisting of abnormal, ectatic, enlarged and coiled arterial or venous capillaries were defined as angiodysplasia.2 Information on the size, localization, and the number of angiodysplasias, comorbid diseases, use of anticoagulant or antithrombotic drugs, presence of diverticular disease and other clinical features were recorded by examining the medical records of the patients. Lesions characterized by pulsatile bleeding but without mucosal defects were generally classified as Dieulafoy lesions and these patients were not included in the study group. Patients with angiodysplasia were divided into two groups according to their bleeding status (bleeding angiodysplasia, non-bleeding angiodysplasia), and their clinical features were compared and risk factors affecting bleeding were analyzed. The cases with active bleeding or with findings of bleeding on endoscopy/colonoscopy examination were considered as "bleeding angiodysplasia".

Treatment and management of gastrointestinal bleeding due to angiodysplasia is still difficult due to the lack of any treatment guideline and varies from center to center. As in many clinics, endoscopic treatments are the first choice in patients with active bleeding or bleeding symptoms in our unit. Coagulation of vascular lesions was performed with argon plasma coagulation (APC) in our patients who were followed up with acute bleeding. In order to reduce the risk of perforation and complications especially in right colon angiodysplasias, submucosal saline with adrenaline was injected to create a fluid cushion in the colon before APC treatment. Hemoclip application was performed in patients, as deemed necessary after APC. There was no recurrence of bleeding as a result of endoscopic treatments. In addition to supportive treatments (iron and blood transfusion) in patients without acute bleeding but with recurrent anemia, endoscopic procedures (APC, hemoclip, endoscopic band ligation) were performed when necessary, particularly in cases with non-multifocal angiodysplasia.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Q-Q and histogram plots were used to determine whether variables were normally distributed. Data are given as median (1st quartile–3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Non-normally distributed variables were analyzed with the Mann-Whitney U test. Categorical variables were analyzed with Pearson's chi-square tests or Fisher's exact tests. Logistic regression analysis (forward conditional method) was performed to determine significant risk factors associated with bleeding. Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

In the study, it was determined that 44 (2.02%) of the 2177 retrospectively-evaluated patients were diagnosed with angiodysplasia. Of the 44 patients in the study group, 24 (54.55%) were male, 20 (45.45%) were female, and the mean age of the study group was 69.12 ± 10.20 (range 41–85) years. Bleeding was detected in 25% (n=11) of patients with angiodysplasia. There was no significant difference between patients with and without bleeding in terms of age ($p = 0.330$), gender ($p = 0.727$), angiodysplasia number ($p = 0.090$), angiodysplasia location ($p = 1.000$), angiodysplasia size ($p = 0.377$), acetylsalicylic acid (ASA) use ($p = 0.080$), antithrombolytic use ($p = 0.080$), nonsteroidal anti-inflammatory drugs (NSAIDs) use ($p = 0.457$), presence of comorbidity ($p = 0.558$), presence of diverticulum ($p = 1.000$), PT ($p = 0.058$), aPTT ($p = 0.382$), iron ($p = 0.139$), ferritin ($p = 0.103$), BUN ($p = 0.149$) and creatinine ($p = 0.467$). The frequency of anticoagulant use was found to be significantly higher in patients with bleeding angiodysplasia ($p = 0.016$). It was found that the frequency of having heart disease was higher in patients with bleeding than those without ($p = 0.008$). Hemoglobin ($p = 0.001$), hematocrit ($p < 0.001$), platelet levels ($p = 0.009$) and total iron binding capacity ($p = 0.036$) were found to be significantly lower in patients with bleeding angiodysplasia

(Table 1, Figure 1).

Table 1 Summary of patients characteristics and laboratory measurements with regard to bleeding

	Bleeding			
	Absent (n=33)	Present (n=11)	Total (n=44)	p
Age	71	71	71	0.330
Gender				
Male	17 (51.52%)	7 (63.64%)	24 (54.55%)	0.727
Female	16(48.48%)	4 (36.36%)	20 (45.45%)	
Number of angiodysplasia				
1-3	28 (84.85%)	6 (54.55%)	34 (77.27%)	0.090
>3	5 (15.15%)	5 (45.45%)	10 (22.73%)	
Location				
Gastric	13 (40.63%)	4 (36.36%)	17 (39.53%)	1.000
Duodenum	1 (3.13%)	1 (9.09%)	2 (4.65%)	0.451
Colon	18 (56.25%)	8 (72.73%)	26 (60.47%)	0.480
Size				
1-5 mm	25 (75.76%)	6 (54.55%)	31 (70.45%)	0.377
5-10 mm	7 (21.21%)	4 (36.36%)	11 (25.00%)	
>10 mm	1 (3.03%)	1 (9.09%)	2 (4.55%)	
Anticoagulant use	12 (36.36%)	8 (72.73%)	20(45.45%)	0.080
ASA	5 (15.15%)	1 (9.09%)	6 (13.64%)	**0.016**
Warfarin	2 (6.06%)	5 (45.45%)	7 (15.91%)	
Antithrombolytic	5 (15.15%)	2 (18.18%)	7 (15.91%)	
NSAIDs use	10 (33.33%)	2 (18.18%)	12 (29.27%)	0.457
Comorbidities	29 (87.88%)	11(100.00%)	40 (90.91%)	0.558
Diabetes mellitus	3 (9.09%)	2 (18.18%)	5 (11.36%)	0.586
Hypertension	12 (36.36%)	1 (9.09%)	13 (29.55%)	0.132
Cirrhosis	6 (18.18%)	4 (36.36%)	10 (22.73%)	0.237
Coronary artery disease	6 (18.18%)	1 (9.09%)	7 (15.91%)	0.659
Heart diseases	4 (12.12%)	6 (54.55%)	10 (22.73%)	**0.008**
Renal diseases	1 (3.03%)	1 (9.09%)	2 (4.55%)	0.442
Malignancy	4 (12.12%)	0 (0.00%)	4 (9.09%)	0.558
Others	13 (39.39%)	4 (36.36%)	17 (38.64%)	1.000
Diverticulum	6 (18.75%)	2 (18.18%)	8 (18.60%)	1.000
Hemoglobin	11.5	7.15	9.8	**0.001**
Hematocrit	34.5	22.9	30.2	**<0.001**
Platelet (x1000)	260	122.5	242	**0.009**
PT	12.9	16.65	13	0.058
aPTT	30.2	29.2	29.7	0.382
INR	1.09	1.42	1.15	**0.004**
Ferritin	14.15	75	16.3	0.103
Iron	44	72	49.5	0.139
Total iron-binding capacity	335	164	307	**0.036**
BUN	17	32	18	0.149
Creatinine	0.80	0.98	0.80	0.467

Data are given as median for continuous variables according to normality of distribution and as frequ (percentage) for categorical variables. Bold values denote the lack of statistically significant difference betv groups.

ASA: acetylsalicylic acid, NSAIDs: nonsteroidal anti-inflammatory drugs, PT: Prothrombin time, aPTT: activate partial thromboplastin time, INR: international normalized ratio, BUN: blood urea nitrogen

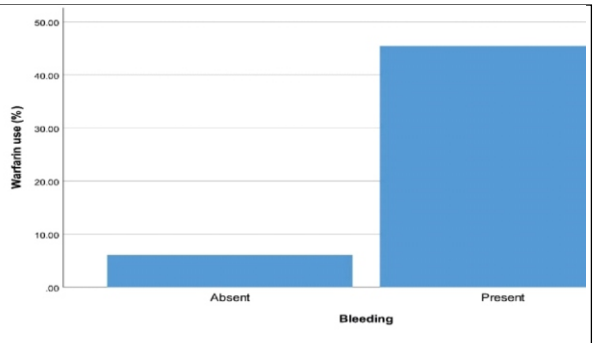

Figure 1 Anticoagulant therapy concerning bleedin

We performed logistic regression analysis to determine significant risk factors associated with bleeding. We found that patients using warfarin had a 12.917-fold higher risk of bleeding than non-users (OR: 12.917, 95% CI: 2.014 - 82.830, p = 0.007). Other variables included in the model, age (p = 0.196), gender (p = 0.326), number of lesions (p = 0.063), gastric lesion (p = 0.880), duodenal lesion (p = 0.472), colonic lesion (p = 0.947), size of lesion (p = 0.789), NSAIDs use (p = 0.631), hypertension (p = 0.163), cirrhosis (p = 0.179), coronary artery disease (p = 0.448) and heart diseases (p = 0.207) were found to be non-significant

(Table 2).

Table 2 . Significant risk factors of the bleeding, multiple logistic regression analysis

	β coefficient	Standard Error	p	Exp(β)	95.0% CI for Exp(β)	
Warfarin use	2.559	0.948	0.007	12.917	2.014	82.830
(Constant)	-1.642	0.446	<0.001	0.194		

Dependent Variable: Bleeding; Nagelkerke R^2=0.255; Correct prediction=81.82%

CI: Confidence Interval

DISCUSSION

Although gastrointestinal angiodysplasias can cause life-threatening massive bleeding, the reason why angiodysplasias tend to bleed in some individuals and not in others has not been fully elucidated.8 In this retrospective study, we determined the clinical features of gastrointestinal angiodysplasia patients according to their bleeding status and risk factors affecting bleeding were assessed. We found that the use of warfarin was the only independent risk factor that was associated with bleeding in patients with gastrointestinal angiodysplasia.

We do not yet have certain information about the true prevalence of angiodysplasia. In the majority of patients, angiodysplasia is diagnosed incidentally since they are often asymptomatic; thus, it is usually a difficult diagnosis because it requires endoscopy. In our study, the prevalence of angiodysplasia among patients evaluated by endoscopy/colonoscopy was 2.02%. In previous similar studies, the prevalence of angiodysplasia among patients who underwent gastrointestinal endoscopy was reported to be between 0.4-2.0%.9-12 The frequency we found is close to the range reported in the literature. It should be noted however, that our data were only based on the evaluation of patients at two centers.

Gastrointestinal angioectasia is reported to be frequently seen in elderly people.8 In the study of Tsai et al., 58.3% of colonic angiodysplasia patients were reported to be older than 65 years.9 In the study by Holleran et al., the mean age of patients with angiodysplasia was reported to be 66.9 (35-90) years.13 Similarly, Diggs and colleagues reported that most (73%) of their patients with angiodysplasia were over 60 years of age.11 Similar to the literature, the mean age of patients with angiodysplasia in our study group was 69.12 ± 10.20 years. When colonoscopy and endoscopy examination is performed in elderly individuals for any reason, it will be useful to carefully evaluate them for the presence of angiodysplasia.

In the study by Diggs et al., it was reported that 56% of patients with angiodysplasia had evidence of blood loss.11 In another study, it was reported that the prevalence of bleeding in patients with angiodysplasia was 6.7%.12 However, Tariq et al. reported the prevalence of angiodysplasia-related gastrointestinal bleeding as 0.45%.14 In our study group, the prevalence of bleeding in patients with angiodysplasia was found to be 25%. The excessive differences between studies may be due to variations in patient groups and differences between endoscopy tools and practitioners, and also the diagnostic approach to bleeding.

Little is known about the bleeding-related risk factors of angiodysplasias. Difficulty in making a definitive diagnosis of bleeding is one of the obstacles to the investigation of risk factors. The bleeding may have stopped when the endoscopy was performed, or the bleeding focus may be difficult to detect because it is so small.12 Anticoagulants, low-dose aspirin, NSAIDs, and other non-aspirin acetylsalicylic acid-derived drugs are associated with an increased risk of gastrointestinal bleeding. It has been reported that the use of anticoagulants may be the strongest risk factor for gastrointestinal bleeding,15 and others have suggested anticoagulant, antithrombotic and antiaggregant drugs as inducing factors for bleeding.2 In the study by Tsai et al., it was reported that age, hypertension, atrial fibrillation and inpatient status were important factors associated with active bleeding lesions; however, old age remained as the only significant risk factor in multivariable analysis.9 Tariq and colleagues reported that higher age, African-American race, increased Charlson-Deyo Comorbidity Index, hypertension presence and tobacco use were associated with bleeding risk in patients with angiodysplasia who had end-stage renal

disease.14 In another study, it was reported that the risk of symptomatic angiodysplasia increased with advanced age, heart valve disease, diabetes mellitus, and hyperlipidemia.16 In a population-based study conducted by Diggs et al. which made use of a national endoscopy database, inpatient status, multiple lesions, black race, severe disease, Hispanic ethnicity and being older than 80 years were associated with bleeding risk.11 In the study by Sekino et al., while cardiovascular disease and multiple angiectasias were reported as important risk factors for active bleeding, it was also reported that drug use was not associated with bleeding risk.17 Interestingly, a study by Jehangir et al. found that aortic valve disease was an independent factor increasing bleeding risk in angiodysplasia.18 Furthermore, greater angiodysplasia count and inhibition of primary hemostasis,19 and advanced age, heart disease, use of anticoagulant drugs, multiple lesions and small lesions have been associated with active bleeding.12 Finally, a study by Nishimura et al. reported that all of their patients with angiodysplasia had chronic heart disease and used anticoagulant and/or antiplatelet drugs, supporting the aforementioned relationships with medications and bleeding.10 The current study found that the risk of bleeding in patients using warfarin was almost 13 times higher than nonusers. However, no relationship was found between age, gender, number of lesions, gastric lesion, duodenal lesion, colonic lesion, size of lesion, NSAIDs use, hypertension, cirrhosis, coronary artery disease and heart diseases. As demonstrated by our review of the literature, there are many differences regarding the bleeding risk factors in patients with gastrointestinal angiosplasia. The differences in patient profiles, research designs and the number of patients covered by the studies, as well as the quality of data collection in retrospective studies are factors that could cause different results. Additionally, in relation with data quality and patient count, the numbers and types of variables included in multivariable models created in each study may have affected the results. While increasing age and heart diseases were important risk factors for bleeding angiodysplasia in many studies, they were not identified as risk factors in the current study. On the other hand, we found that the use of warfarin was the only parameter that significantly increased the risk of angiodysplasia bleeding.

Although the cause and mechanism of angiodysplasia development are not fully understood yet, various theories have been put forward.5 It has been reported that they may develop secondary to chronic low-grade obstruction of the submucosal veins, together with proliferation due to increased vascular endothelial growth factor (VEGF).3 Another proposed theory is that muscle contractions in the muscularis propria may trigger chronic hypoxemia that will lead to angiogenesis mediated by chemical agents such as VEGF. On the other hand, another theory states that proliferation of vessels can be induced by primary or secondary reduction of high molecular weight vWF multimers, which increase VEGF-dependent angiogenesis and decrease platelet aggregation.2

Although our study includes data from four years of patients from two centers, our research has several limitations. The first of these is that the research has a retrospective design. The level of evidence we would have obtained with a prospective study could have been higher. Another limitation is the possibility of unreported angiodysplasia cases during endoscopy/colonoscopy performed for any reason. Another limitation is the inclusion of the results of only a small number of patients from two centers in a single country and the absence of a control group. Therefore, the results of the study cannot be generalized to general populations. On the other hand, another limitation of ours is that the time period in which the data were obtained is limited to four years. However, this was necessary due to changes in endoscopy devices and operators prior to the four-year study period. Another limitation of ours is that the treatment features could not be evaluated in cases of angiodysplasia with bleeding. Despite these limitations, our study is remarkable in that it shares the clinical characteristics of patients with angiodysplasia from two centers and shares detailed results with regard to bleeding risk factors, and therefore, could be valuable as clinical guidance.

CONCLUSION

In conclusion, it can be said that the use of warfarin is associated with the risk of bleeding in cases of gastrointestinal angiodysplasia. We also found that the mean age of patients with angiodysplasia was high; however, bleeding was not associated with age in this study. Physicians should be aware of the possibility of incidentally encountering angiodysplasia during gastrointestinal endoscopy examinations to be performed in elderly individuals. In addition, it was concluded that it would be beneficial to elevate clinical awareness against gastrointestinal bleeding in patients with angiodysplasia. Community-based, prospective and more comprehensive studies are needed in order to elucidate factors affecting bleeding in patients with gastrointestinal angiodysplasia.

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Authorship Contributions:

Concept - B.Y.K; Design - B.Y.K, H.D; Supervision- B.Y.K, İ.Y; Materials - H.D, Data collection &/or processing - B.Y.K, H.D; Analysis and/or interpretation - İ.Y; Literature search - B.Y.K, H.D; Writing - B.Y.K, H.D, İY; Critical review - H.D, İ.Y.
All authors discussed the results and commented on the manuscript.

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