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Predictors of colonic diverticulosis in non-elderly patients

Abdurrahman Şahin[1], Mustafa Cengiz[2], Oktay Sarı[3]

[1]Gaziosmapasa University Faculty of Medicine, Department of Gastroenterology, Tokat, Turkey
[2]Gulhane Training and Research Hospital, Department of Gastroenterology, Ankara, Turkey
[3]Gulhane Training and Research Hospital, Department of Department of Family Medicine, Ankara, Turkey

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ABSTRACT

Aim: To investigate the clinical and laboratory features patients under aged 65 years with diverticulosis and to compare them to subjects with no diverticula.

Material and Method: This retrospective case-control study included subjects aged under 65 years who underwent a colonoscopy in the period from January 2016 to June 2018 for diverse indications. Patients with diverticulosis as detected by a colonoscopy were compared to patients without diverticulosis. The comparison parameters included demographic data, comorbidities, and laboratory parameters, including a complete blood count, blood biochemistry, erythrocyte sedimentation rate (ESR), and C-reactive protein.

Results: The study included 129 patients with diverticulosis and age and sex-matched 130 patients with no diverticula. Diverticula were predominantly left-sided in 64.3%, right-sided in 9.3%, and bilateral in 26.4%. Hypertension was more prevalent among patients with diverticulosis compared to control subjects (31% vs 17%, p<0.01). The median ESR was higher in diverticulosis group than in control group (13±1.6 mm/h vs 9±0.9 mm/h, p=0.01). The mean creatinine was higher (0.86±0.25mg/dL vs 0.76±0.19 mg/dL, p<0.01) and the mean albumin was lower (4.3±0.4 g/dL vs 4.5±0.3 g/dL, p<0.01) in diverticulosis group compared to control group. Hypertension, ESR, creatinine and albumin were independent predictors of the presence of diverticulosis in univariate and multivariate logistic regression analysis.

Conclusion: It is important to determine the characteristic features of asymptomatic patients with diverticulosis in earlier ages. The presence of hypertension, in conjunction with high creatinine and low albumin values increase the probability of the presence of asymptomatic colonic diverticula.

Keywords: Albumin, colonic diverticula, creatinine, hypertension, non-elderly

INTRODUCTION

Colonic diverticulum is the herniation of the mucosal and submucosal layers outward due to deficiency in the muscle layer of colon. Although diverticulosis is an anatomical definition indicating the presence of a single or multiple diverticula in the colon in asymptomatic individuals, diverticular disease is defined as the presence of symptoms associated with diverticula and is observed in approximately 25% of patients(1). While several complications including diverticulitis, bleeding, obstruction, and perforation may develop in the course of disease in some of the cases, most of the symptomatic patients remain complication free for a long time(2). Older age, genetic predisposition, constipation, high intake of red meat, low-fiber diet, low level of physical activity, obesity and smoking have been linked as predisposing factors for the development of diverticulosis(3, 4).

Geographical location influences diverticulosis prevalence, and is more common in Western countries than in Africa and Asia. In Western countries, diverticulosis affects around 30% at 65 years, and up to 66% in those aged 80 years or older(5). On the other hand, the prevalence of colonic diverticulosis has been reported between 1.9% and 20% from Asian countries and the Mediterranean area(6, 7). Moreover, the location of diverticula varies among nations. While a dominancy of left-sided location is seen in Western populations, right-sided location is more prevalent in Asia.

Diverticulosis is an age-related disorder that is rare under age 40 years and is found in more than one-half of adults over the age of 65 years in Western countries. Diverticulosis can occur in younger ages in several connective tissue disorders like Marfan or Ehlers-Danlos

Corresponding Author: Abdurrahman Sahin, arahmansmd@gmail.com
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syndromes(8). Right-sided diverticulosis can also appear in younger ages and presents predominantly with gastrointestinal bleeding.

Most of the studies about colonic diverticulosis have been carried out on geriatric population. There is little known about colonic diverticulosis in patients under 65 years old. In this study, we aimed to investigate the clinical and laboratory features of patients under 65 years who developed diverticulosis and to compare them to age and sex-matched subjects with no diverticula.

MATERIAL AND METHOD

Study Subjects

This retrospective case-control study included subjects aged between 18 and 64 years who underwent a colonoscopy for several indications, mostly for colorectal cancer screening, from January 2016 to June 2018. Patients who had diverticulosis on colonoscopic examination were recorded. Sex and age-matched subjects who had no diverticula on colonoscopic examination were also recorded. Subjects who had a history of colitis, colorectal cancer, and colonic surgery, subjects attended to the hospital with lower gastrointestinal bleeding or acute diverticulitis were excluded. Demographic data, co-morbidities including diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL) and coronary arterial disease (CAD) were recorded. Laboratory parameters, including a complete blood count, blood biochemistry, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were collected from the patients' medical records.

Ethical Considerations

Ethics committee approval was obtained for the study from Firat University Non-Interventional Research Ethics Committee (Date: 19.07.2018, Decision No: 2018/13-18). All the procedures followed were in accordance with the ethical standards of the ethics committee and with the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using the SPSS® statistical package, version 22.0 (SPSS Inc., Amrok, NY, USA) for Windows®. Categorical variables are presented as frequencies and percentages. Categorical variables were appropriately analyzed by the Chi-square test or Fisher's exact test. The Shapiro-Wilk test was used to measure the normality of the data distribution for continuous variables. All the normally distributed continuous variables were presented as the mean and standard deviation while the non-normally distributed continuous variables were presented as the median and standard error of mean. The Mann-Whitney U test was applied for continuous variables without a normal distribution analysis, where appropriate. Univariate and multivariate logistic regression analyses were used to analyze the factors influencing the presence of colonic diverticulosis. In all analyses, the significance level was set at 0.05.

RESULTS

A total of 129 patients aged <65 years with diverticulosis and 130 patients aged <65 years who had no diverticula were recruited into the study. While the mean age of the diverticulosis group was 54.7±7.5 years, the mean age of control subjects was 54.1±7.8 years (p=0.52). Seventy-eight of subjects (61%) in diverticulosis group and 75 of control subject (58%) were male (p= 0.65). Diverticula were located at left colon in 83 subjects (64.3%), at right colon in 12 subjects (9.3%) and pancolonic in 34 subjects (26.4%).

Diabetes was found in 19 subjects with diverticulosis (15%) and, 23 subjects who had no diverticula (18%) (p=0.52). Likewise, hyperlipidemia did not differ between diverticulosis group and control group [24(19%) vs 16(12%), p=0.16]. Coronary arterial disease was another disorder that didn't differ between two groups [10(8%) vs 8(6%) respectively, p>0.61]. On the other hand, HT was more prevalent among subjects with diverticulosis compared to subjects without diverticulosis [40(31%) vs 22(17%), p<0.01].

The laboratory characteristics of the two groups of participants are presented in **Table 1**. The median erythrocyte sedimentation rate was higher in the diverticulosis group than in the control group (13±1.6 mm/hour vs 9±0.9 mm/hour, p=0.01) (**Figure 1**). We could not detect any difference between the groups in terms of CRP (3.4±2.3 mg/L vs 3.0±2.8 mg/L, p=0.15). The mean creatinine value was higher (0.86±0.25mg/dL) in the diverticulosis group when compared to the control group (0.76±0.19 mg/dL) (p<0.01) (Figure 1). On the other hand, albumin was lower in subjects with diverticulosis compared to control subjects (4.3±0.4 g/dL vs 4.5±0.3 g/dL, p<0.01) (**Figure 1**). Other laboratory parameters didn't differ between two groups (for all, p>0.05).

Univariate analysis for the presence of diverticulosis demonstrated that the presence of HT, erythrocyte sedimentation rate, creatinine and albumin were statistically significant independent predictive factors (**Table 2**). Variables that were statistically significant in the univariate logistic regression model were further subjected to a multivariate logistic regression analysis and all of them remained statistically significant independent predictors for the presence of diverticulosis (**Table 3**).

Table 1. Comparison of laboratory features between patients with diverticulosis and patients who had no diverticula

	Patients with tdiverticulosis (n=129)	Patients without diverticulosis (n=130)	p
WBC (x10³/uL)	7302±2259	7100±2011	0.45
Hemoglobin (g/dL)	13.9±1.8	14.3±1.5	0.09
Platelet (x10³/uL)	263±73	257±76	0.55
Fasting blood glucose (mg/dL)	104±30	107±33	0.53
ALT (U/L)*	23±1.3	24 ±1.2	0.43
AST (U/L)*	22±0.8 (18-27)	24±0.8	0.56
GGT (U/L)*	26±3.5	25±6.4	0.16
ALP (U/L)*	72±3.1	72±2.4	0.40
Bilirubin, total (mg/dL)*	0.5±0.04	0.6±0.03	0.11
Blood urea (mg/dL)	32.1± 9.5	30.2±9.8	0.12
Creatinine (mg/dL)	0.86±0.25	0.76±0.19	<0.01
Total protein (mg/dL)	7.3±0.7	7.4±0.6	0.06
Albumin (g/dL)	4.3±0.4	4.5±0.3	<0.01
Triglyceride(mg/dL)*	151±16.2	143±7.8	0.39
LDL (mg/dL)	129± 42	123±35	0.24
HDL (mg/dL)	44±12	45±15	0.69
ESR (mm/h)*	13±1.6	9±0.9	0.01
CRP (mg/L) *	3.4 ±2.3	3.0 ±2.8	0.15

(*) Data are presented as median±SE of mean, WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

Table 2. Univariate logistic regression analysis for predictors of diverticulosis

	B	OR	%95 CI OR	p
Age	0.010	1.010	0.979-1.043	0.524
Sex, male	0.115	1.122	0.683-1.841	0.650
Diabetes mellitus	-0.219	0.804	0.414-1.560	0.518
Hypertension	0.791	2.206	1.222-3.985	0.009
Hyperlipidemia	0.488	1.629	0.820-3.234	0.163
Coronary artery disease	0.248	1.282	0.489-3.358	0.614
White blood cell count	0.000	1.000	1.000-1.000	0.477
Hemoglobin	-0.127	0.881	0.762-1.019	0.088
Platelet	0.001	1.001	0.998-1.004	0.547
Fasting blood glucose	-0.002	0.998	0.990-1.005	0.533
Alanine aminotransferase	-0.006	0.994	0.977-1.011	0.477
Aspartate aminotransferase	-0.012	0.988	0.962-1.015	0.381
Gamma-glutamyl transferase	-0.001	0.999	0.995-1.004	0.759
Alkaline phosphatase	0.004	1.004	0.995-1.012	0.422
Bilirubin, total	-0.073	0.929	0.468-1.846	0.834
Blood urea	0.021	1.021	0.995-1.048	0.120
Creatinine	2.039	7.682	2.459-24.003	<0.001
Total protein	-0.405	0.667	0.439-1.014	0.058
Albumin	-1.072	0.342	0.173-0.677	0.002
Triglyceride	0.002	1.002	0.999-1.004	0.185
Low-density lipoprotein cholesterol	0.004	1.004	0.997-1.011	0.236
High-density lipoprotein cholesterol	-0.004	0.996	0.977-1.016	0.685
Erythrocyte sedimentation rate	0.033	1.033	1.012-1.055	0.002
C-reactive protein	0.005	1.005	0.992-1.018	0.444

Table 3. Multivariate logistic regression analysis for predictors of diverticulosis

	B	OR	%95 CI OR	p
Hypertension	0.876	2.401	1.242-4.642	0.009
Creatinine	2.628	13.852	3.729-51.457	<0.001
Albumin	-0.761	0.467	0.220-0.993	0.048
Erythrocyte sedimentation rate	0.034	1.035	1.010-1.061	0.007

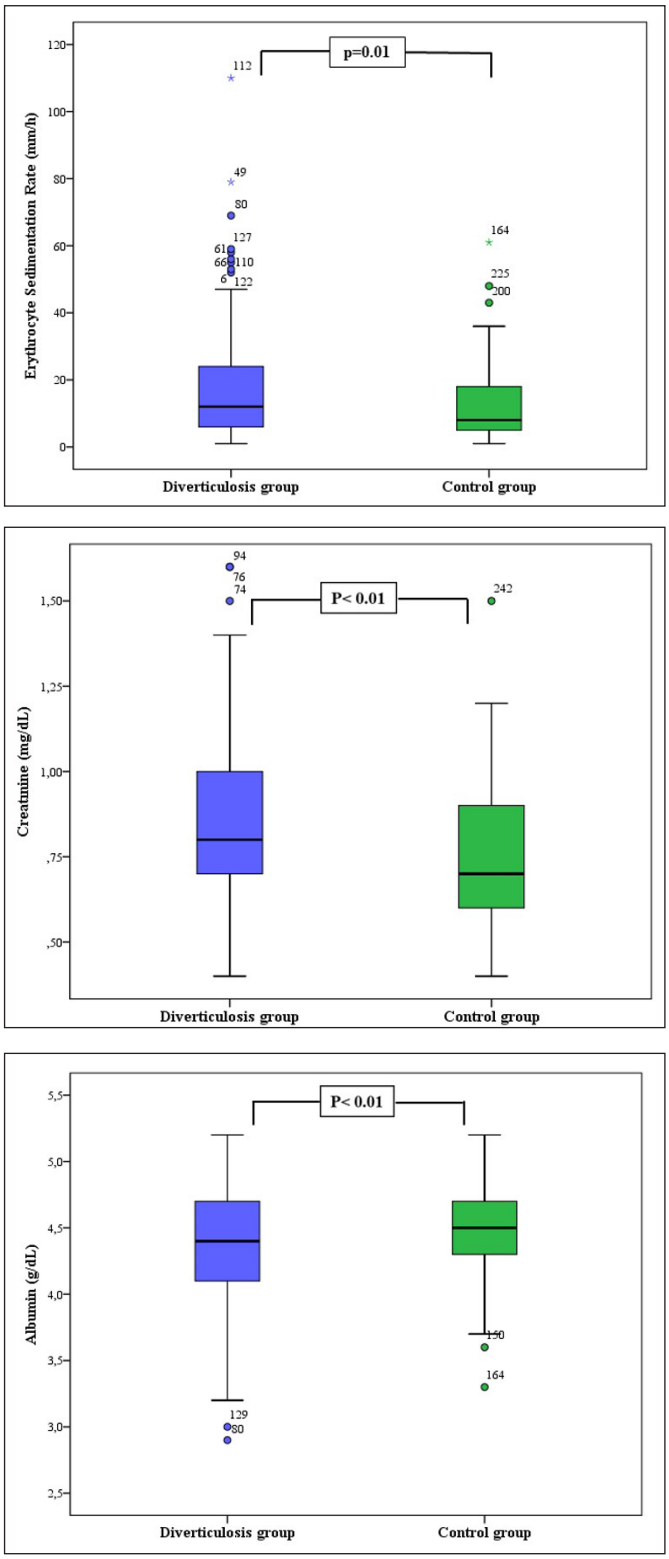

Figure 1. Comparison of erythrocyte sedimentation rate, creatinine and albumin values between diverticulosis group and control subjects

DISCUSSION

Diverticulosis is essentially considered an asymptomatic condition, frequently observed as an incidental finding in patients undergoing radiologic or endoscopic assessment for several indications. Technical advances in radiologic and endoscopic assessment of the colon and widespread use of these tools in the clinical assessment lead to increased diagnosis of colonic diverticulosis. The conventional idea about diverticular disease is that it typically affects older people. Several studies have reported an increased incidence of diverticular disease over time with a meaningful increase in younger aged people (9-11). The incidence of diverticulitis in people aged between 40 and 49 years old increased by 132% from 1980 through 2007 (12). Unlike these results, many time-trend studies demonstrated that there is no increase in the prevalence of symptomatic diverticular disease and hospitalization over time in younger ages (13). Though several studies have been carried out in younger people with symptomatic diverticular disease, especially acute diverticulitis, there is no satisfactory data on the frequency of asymptomatic diverticulosis.

In the current study, we assessed demographic clinical and laboratory features of asymptomatic patients with diverticulosis and, compared with subjects with no diverticula. As stated earlier, right-sided diverticulosis is related with the presentation of diverticulosis in earlier ages of the life, and several reports from Asia give information about the features of subjects with diverticulosis in non-geriatric population. In a prospective study from China on asymptomatic subjects undergoing colonoscopic evaluation that most of them under 70 years old, diverticula were right-sided in two-third of patients with diverticulosis (14). In our study, 64.3% of colonic diverticula were located in the left colon, 9.3% in the right colon, and 26.4% were located bilaterally. The distribution of colon diverticula varies geographically. Left-sided diverticulosis is more prevalent in Western world, Africa and the Mediterranean area. In a previous study from Middle East, 62% of colonic diverticula were located in the left colon and only 13% were located in the right colon (15). In a prospective study from Italy, diverticula were detected in 27.8% of 438 patients undergoing colorectal cancer screening and, 97.8% of diverticula was left-sided (16). Our findings were compatible with the results of studies form the Mediterranean area.

Hypertension is a well-known associated disorder with diverticulosis. In a Japan study on subjects undergoing colonoscopic evaluation aged between 51 and 59 years, HT and DM were observed more frequently in subjects with diverticulosis compared to those without diverticula (17). In the aforementioned study, HT was found to be 31% and 20% between patients with and without diverticula, respectively. Similar results were observed in the Middle East study, and HT, DM and HL were found at higher rates in patients with diverticulosis (15). In addition to the high rate of HT detected as 64% in those with diverticula, it was found that the presence of HT increased the likelihood of colonic diverticulosis by 2.3 times. On the other hand, in a population of aged under 70 years from China, HT was found more prevalent among patients with diverticulosis compared to those with no diverticula (14,17). In the current study, HT, but not DM, was found more prevalent among patients with diverticulosis. On the other hand, we couldn't detect any difference among patients aged over 65 years in terms of HT, DM and HL according to the presence of diverticulosis in our previous study (8). Moreover, a study from Israel showed that DM and hypothyroidism were associated with diverticulosis, while the presence of HT and HL were not (18). Further studies are needed to evaluate the relationship between colonic diverticulosis and associated disorders.

In the comparison of inflammatory markers, although CRP values were similar in both groups, ESR values were higher in patients with diverticulosis. CRP is a useful marker that can be used in the prediction of acute inflammatory conditions such as acute diverticulitis. The fact that our study group consisted of patients with asymptomatic diverticulosis and, the absence of acute inflammation in these patients explains normal CRP values. Leukocytosis, which is another indicator of acute inflammation, was not observed in patients with diverticulosis and, the leukocyte count was similar to the controls. The higher ESR values in patients with diverticulosis may be associated with the ongoing low level of systemic inflammation. C-reactive protein that is a direct acute phase reactant, shows short term alterations related to acute inflammation, while the change in ESR, which is an indirect indicator of inflammation, requires longer time.

In the current study, we found higher values of creatinine and lower albumin values among patients with diverticulosis than those had no diverticula. These results were compatible with our previous study on geriatric patients with diverticulosis (7). There is scarce data about laboratory parameters of subjects with diverticulosis on the literature. The underlying pathological mechanisms that cause the formation of colonic diverticula are likely to be the result of complex interactions among age, diet, colonic microbiota, genetic factors, colonic motility, and changes in colonic structure (19). Several metabolic alterations occur in extracellular matrix components of the colon as a result of aging process. Two major extracellular matrix components, collagen and elastin, have been

found to be altered in diverticulosis. The smaller, more densely packed collagen fibrils and an overexpressed cross linking of collagen molecules with increased rigidity and a subsequent loss of tensile strength occur (20). An increase of elastic fibers confined to the longitudinal muscle layer results in the thickening of the colonic wall (21). Chronic kidney disease (CKD) is characterized by the development of renal fibrosis, which is the inevitable consequence of continuous accumulation and activation of myofibroblasts and extracellular matrix deposition in interstitial space leading to organ dysfunction. Fibrosis occurs in every type of CKD, regardless of the cause, and it contributes to a progressive and irreversible loss of renal function (22). It is suggested that pathogenetic mechanisms that lead to the formation of diverticula are similar to the mechanisms that lead to the development of CKD. Thus, an identical fibrotic process may either cause the development of colon diverticulum and impairment of renal functions. Lower albumin values that were found in diverticular group may be associated with dietary factors or as a result of ongoing low grade inflammation.

There are some limitations to our study that is mainly associated with its retrospective nature. Several pathogenic life-style factors that reported to be associated with colonic diverticulosis; in particular, physical activity, familial and hereditary factors, obesity, and a detailed quantitative dietary history with regard to fiber, red meat and fat intake could not be incorporated into the analyses due to the study design. This is a single-center, retrospective, case-control study with a limited number of subjects undergoing colonoscopic examination. Future prospective studies are necessary to confirm the results of the present study. Third, self-election bias of the participants in the study might exist because, all of the study subjects intended to pay more attention to their health condition. Thus, the current findings cannot be generalized for all subjects under 65 years.

CONCLUSION

Consequently, the diagnosis of colonic diverticulosis has been increasing in younger aged people recently. It is important to determine the demographic, clinical and laboratory features that can help to indirectly identify asymptomatic patients with diverticulosis. Patients with HT was found to have an increased risk for the development of colonic diverticulosis in this study. Higher ESR and creatinine values in conjunction with lower albumin values were found as laboratory features of patients with diverticulosis. Further studies are needed to define the characteristic features that will enable the identification of patients with diverticulosis at an earlier age.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained for the study from Fırat University Non-Interventional Research Ethics Committee (Date: 19.07.2018, Decision No: 2018/13-18).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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