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ORIGINAL ARTICLE

Evaluation of Patients with Diarrhea Applying to the Outpatient Gastroenterology Clinic of Research Hospital

Çağlayan Merve Ayaz[1]
ORCID: 0000-0003-2574-8683

Batuhan Başpınar[2]
ORCID: 0000-0003-3143-2642

Ertuğrul Kayaçetin[2]
ORCID: 0000-0002-8822-3991

[1]Department of Infectious Diseases and Clinical Microbiology, Ankara City Hospital, Ankara, Turkey.

[2]Department of Gastroenterology, Ankara City Hospital, Ankara, Turkey.

Corresponding Author: Çağlayan Merve Ayaz
Infectious Diseases and Clinical Microbiology Clinic, Ankara City Hospital, Ankara, Turkey.
E-mail: merve.ayz@hotmail.com

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ABSTRACT

Objectives: Diarrhea is a common health problem and may occur for many infectious and non-infectious causes. In this study, it was aimed to investigate the causes, methods used in diagnosis and the results obtained in patients who applied to the gastroenterology clinic with the complaint of diarrhea.

Materials and methods: 187 patients who presented with diarrhea between 01.11.2019-01.11.2020 were included in this study.

Results: Acute diarrhea was detected in 32 (17.1%) out of 187 patients, persistent in 34 (18.2%), and chronic diarrhea in 121 (64.7%). The cause of diarrhea was detected in 148 (79.1%) patients. Infectious cause in 66 (%44.6) patients; inflammatory bowel disease (IBD) in 41 (27.7%) patients; irritable bowel syndrome (IBS) in 22 (14.9%) patients and less frequently as other diagnose were listed. The cause of diarrhea was detected in 73.6% of patients with chronic complaints, and this rate was 87.5% in acute diarrhea; and 91.2% of those presenting with persistent diarrhea ($p = 0.04$). Lower C reactive protein levels were found in irritable bowel syndrome compared to other diarrheal causes ($p<0.001$). It was observed that anti-infective treatment was used more frequently in acute and persistent diarrhea compared to chronic diarrhea ($p <0.001$).

Conclusion: Although application to outpatient clinics were more frequent due to chronic diarrhea, acute and persistent diarrhea were also not rare (35.3%). The reason to explain diarrhea has been found in the majority of patients. Infectious induced diarrhea was seen as the most common cause, it was followed by IBD and IBS, respectively. When prescribing anti-infective agents, clinical, laboratory and microbiological results should be considered and inappropriate drug use should be avoided.

Keywords: Diarrhea, Gastroenterology, Anti-Infective Agents

INTRODUCTION

Diarrhea is a common problem characterized by soft, watery stools and increased frequency of bowel movements. Etiology can stem from many infectious or non-infectious causes [1]. Although it usually does not last longer than a few days, in patients with prolonged diarrhea irritable bowel syndrome (IBS), chronic infections, systemic diseases (such as hyperthyroidism, diabetes), inflammatory bowel diseases (IBD), malignancies, celiac disease and specific enzyme deficiencies should be investigated [2,3].

Acute infectious diarrhea is the 5th most common cause of death from all causes in the World [4]. It is usually self-limited. Only some infections require anti-infective therapy. Appropriate use of diagnostic tests and treatments minimizes potentially unnecessary costs, reduces adverse events,

optimizes clinical outcomes, and limits antibiotic resistance [5]. Diarrhea lasting longer than 14 days but less than four weeks is classified as persistent diarrhea and bacterial and protozoal infections often take place in the etiology [6,7]. Chronic diarrhea (≥ four weeks) affects approximately 5.0% of the population at a given time and is a common problem often caused by non-infectious causes in developed countries [2].

When the underlying diseases, symptoms, examination findings, and histories of the patients are combined, acute diarrhea can be diagnosed in most of the cases. However, advanced diagnostic methods may need to be used in persistent and chronic diarrhea [2]. Stool culture, examination of fresh stool sample under light microscopy, investigation of viral agents, blood tests (hemogram, kidney and liver function tests) and inflammatory markers such as C reactive protein (CRP), erythrocyte sedimentation rate (ESR) are used for initial work-up. Imaging and endoscopic methods are also used when necessary.

Although treatment constitutes the symptom-relieving medications in most cases, Antibacterial, antiprotozoal and anthelmintic drugs can be used in selected cases. In non-infectious diarrhea, treatment of the underlying causes should be employed. In this study, it was aimed to investigate the epidemiological history, causes of diarrhea, methods used in diagnosis and treatments given to patients who applied to the gastroenterology clinic with diarrhea.

MATERIALS AND METHODS

Study Design

This retrospective cross-sectional study was conducted in gastroenterology clinic Ankara City Hospital. Patients who applied to the Gastroenterology clinic between Nov,1, 2019 and Nov,1, 2020 with the complaint of diarrhea were examined. A total of 599 patients were evaluated for eligibility for the study. Among these patients, 187 patients aged ≥18 years who presented with diarrhea were included in the study (Figure 1). Patient data were obtained from the hospital automation system. The data obtained from the hospital automation system for the patients involved in the study include age, gender, presence of concomitant disease, duration and nature of diarrhea, recent use of new drugs, history of eating out, presence of the same symptom in family members, biochemical, microbiological, serological and pathological studies, imaging methods, presence of an interventional procedure due to diarrhea, the cause of diarrhea determined as a result of the examinations, and the drugs preferred in the treatment are included.

Stool samples evaluated macroscopically in terms of color, consistency, quantity, form, odor, blood and presence of mucous. Microscopic examination is a diagnostic tool for defining protozoa, helminths, and fecal leukocytes, erythrocytes. Fresh stool sample was used for detecting for motile organisms (parasites, helminths, cysts and trophozoites).

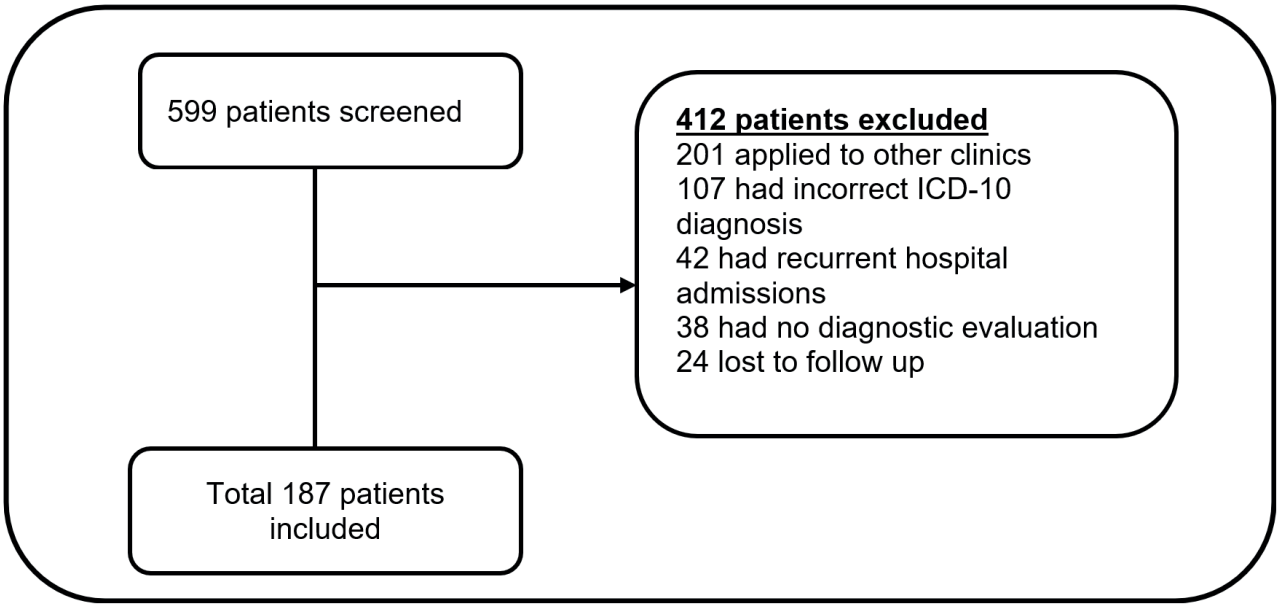

Figure 1. Study profile

A stool culture method was used to identified bacterial and fungal causes. A stool antigen test (monoclonal immunoassays) for detection of *Helicobacter pylori* was performed for making the diagnosis. Nucleic acid tests such as polymerase chain reaction (PCR) were selected to detect *rotavirus* in the stool. Stool samples of only patients with diarrhea should be studied and no checking should not be performed after treatment. Most *Clostridioides difficile* strains produce both A and B toxins, but some strains produce only A toxin or B toxin. Toxin B is clinically important. Monoclonal immunoassays test performed for both toxins [8].

Leukocytosis, defined as an elevated white blood cell (WBC) count greater than 12,000/μL, and WBC count of <4,000/μL was considered leukopenia. C reactive protein >5 mg/L; ESR >20 mm/hr, lactate dehydrogenase >245 U/L, alanine transaminase (ALT) >50 U/L and aspartate transaminase (AST) >35 U/L were considered higher than normal.

Ethical permission of the study was obtained from Ankara City Hospital Clinical Research Ethics Committee (06.01.2021/20-1344).

Statistical Analysis

SPSS Statistics 24 (IBM, New York, ABD) program was used in the comparison of statistical data. Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean, ± standard deviation, median, and minimum-maximum for numerical variables. Pearson chi-square and Fisher's Exact test for comparison of categorical data between groups; Kruskal-Wallis tests were used for comparisons between independent groups for numerical variables that were not normally distributed, respectively. The statistical significance level in the analyzes was accepted as p value < 0.05.

RESULTS

Given the eligibility for the study, 599 patients were screened and 187 patients who met the inclusion criteria were included in the study. Of 187 patients, 104 (55.6%) were male and 83 (44.4%) were female. The median age was 38.0 (min:18.0-max: 81.0).

Underlying disease was present in 127 (67.9%) patients. Diabetes (6.4%) and hypertension (5.4%) were most common. Nine (4.8%) patients had a history of new drug use for the treatment of underlying diseases. Immunosuppression was present in 8 (4.3%) patients and these patients were using immunosuppressive drugs due to underlying malignancy, rheumatological disease or organ transplantation.

All of the patients (100.0%) were questioned for presence of similar symptoms in their family, suspicious food and water consumption, but no similar complaints were detected in the family or in the environment of any patient. It was found that only 1 (0.5%) patient had a history of eating out.

When the patients are evaluated according to the duration of diarrhea; acute diarrhea was detected in 32 (17.1%) patients, persistent in 34 (18.2%) patients, and chronic in 121 (64.7%) patients.

In the macroscopic examination of stool, 128 (68.4%) stool of patients were bloodless-mucous-free; bloody-mucous diarrhea was observed in 28 (15.0%) patients. In microscopic examination, leukocytes and erythrocytes were detected in 59 (31.6%) and 24 (12.8%) patients, respectively. Of 162 (86.6%) patients for whom fresh stool samples were requested, protozoal parasites were seen in 14 (8.6%) out of them (8 *Blastocystis spp* cysts, 3 *Entamoeba histolytica* cysts, 3 *Giardia intestinalis* cysts) and increased yeast was seen in 3 (1.8%) out of them. There was growth in only one patient's stool sample sent for culture (*Salmonella spp*).

Helicobacter pylori antigen test and *Clostridioides difficile* toxin B were positive in 12 (6.4%) and in 9 (4.8%) patients, respectively.

Cytomegalovirus (CMV) (>80 copies/mL) was detected in blood of four patients and *rotavirus* was detected in stool of two patients by PCR. The comparison of the variables according to the duration of diarrhea was presented in Table 1.

Acute kidney injury secondary to diarrhea developed in 4 (2.1%) patients. Abdominal ultrasound and computed tomography (CT) were performed, if needed, and pathological findings related to the intestines were thickening of the intestinal wall, free fluid between the intestines, dilatation and edema in the intestinal loops. No diagnostic result could be reached in the abdominal CT of 8 (27.6%) patients.

Table 1. Characteristics of patients by duration of diarrhea[α]

	Acute diarrhea (n, %)	Persistent diarrhea (n, %)	Chronic diarrhea (n, %)	p value
Age, years (min-max) (n=187)	36.0 (18.0-77.0)	44.5 (21.0-81.0)	37.0 (18.0-81.0)	0.38
Sex (female) (n=187)	15 (46.9)	13 (38.2)	55 (45.5)	0.72
Underlying disease* (n=187)	16 (50.0)	10 (29.4)	33 (27.3)	0.046
Immunosupression* (n=187)	1 (3.1)	4 (11.8)	3 (2.5)	0.07
New drug use* (n=187)	3 (9.7)	-	6 (5.0)	0.15
Fresh wet stool examination* (n=167)				
Protozoa*	2 (14.3)	5 (35.7)	7 (50.0)	0.21
Erythrocyte*	4 (15.4)	4 (12.5)	16 (14.7)	0.94
Leukocyte*	12 (46.2)	13 (40.6)	34 (31.2)	0.28
Clostridioides difficile toxin B* (n=88)	1 (7.1)	3 (25.0)	5 (8.1)	0.16
Leukocytosis WBC>12,000/μL* (n=183)	5 (16.7)	4 (11.8)	20 (16.8)	0.77
Leukopenia WBC<4,000/μL* (n=183)	1 (3.3)	1 (2.9)	3 (2.5)	1.00
ALT>50 U/L or AST>35 U/L* (n=183)	3 (10.0)	2 (5.9)	5 (4.2)	0.40
CRP >5 mg/L* (n=154)	11 (50.0)	15 (53.6)	44 (42.3)	0.51
ESR >20 mm/hr* (n=72)	4 (40.0)	5 (35.7)	10 (20.8)	0.31
LDH >245 U/L* (n=142)	5 (23.8)	5 (17.9)	11 (11.8)	0.33
Helicobacter pylori* (n=48)	2 (28.6)	1 (20.0)	9 (25.0)	1.00
Abdominal ultrasound[β] (n=78)	3 (33.3)	1 (8.3)	8 (14.0)	0.31
Abdominal CT[β] (n=29)	-	3 (60.0)	18 (75.0)	NA
Abdominal MRI[β] (n=17)	1 (50.0)	-	11 (73.3)	NA
Endoscopy[β] (n=65)	3 (75.0)	6 (85.7)	40 (74.1)	0.85
Colonoscopy[β] (n=104)	9 (90.0)	12 (80.0)	51 (64.6)	0.17
Biopsy[β] (n=84)	7 (100.0)	9 (81.8)	59 (89.4)	0.66
Cause of diarrhea[x] (n=187)	28 (87.5)	31 (91.2)	89 (73.6)	**0.04**
Use of antimicrobial drug* (n=166)	20 (62.5)	20 (62.5)	32 (31.4)	**<0.001**

[α]Numbers and percentages belong to columns. *Represents the existence of the specified variables. [β]Represents the presence of pathological result. [x]Represents patients whose cause can be found.

n: number, %: percent, min: minimum, max: maximum, WBC: White blood cell, ALT: Alanine transaminase, ASR: Aspartate transaminase, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, CT: Computed tomography, MRI: Magnetic resonance imaging, NA: Not applicable.

Of the patients who underwent endoscopy, 20 (30.8%) had antral gastritis, 19 (29.2%) had pangastritis and 16 (24.6%) had normal findings. Duedonitis, alkaline reflux gastritis and esophagitis were detected less frequently or accompanied by other diagnoses. Of the patients who underwent colonoscopy, 32 (30.7%) had normal findings, 21 (20.2%) had ulcerative colitis, 11 (10.6%) non-specific colitis, 10 (9.6%) adenoma/polyp, 8 (7.7%) had ileocolitis. Diverticular disease, edematous appearance, hemorrhoids and mass were detected less frequently or accompanying other diagnoses.

Biopsy was performed in 84 (44.9%) patients who underwent endoscopy and colonoscopy, if clinically necessary. Of the biopsy results of the patients, 15 (17.9%) had ulcerative colitis, 11 (13.1%) had colitis that cannot be classified as pathologically, 11 (13.1%) had *H. pylori*, 11 (13.1%) had chronic gastritis, 9 (10.7%) had Crohn's disease and 9 (10.7%) had normal findings. Ileitis, collagenous colitis, adenoma/polyp, duodenitis, adenocarcinoma, findings compatible with celiac disease, and edema in the colon were detected less common or accompanying other diagnoses.

The cause of diarrhea was detected in 148 (79.1%) patients as a result of clinical findings, and laboratory, microbiological, pathological examinations, and the cause could not be found

Table 2. The causes of diarrhea (n=148)

	n (%)		n (%)
Infectious causes*	66 (44.6)	**Irritable bowel syndrome**	22 (14.9)
Protozoa	14 (21.2)	**Others***	
Clostridioides difficile	9 (13.6)	Celiac disease	5 (3.4)
Rotavirus	2 (3.0)	Malignancies	4 (2.7)
Salmonella spp	1 (1.5)	Drug-related diarrhea	3 (2.0)
Thought to be infectious	42 (63.6)	Adenoma/polyp	3 (2.0)
Inflammatory bowel diseases*	41 (27.7)	Chronic pancreatic insufficiency	2 (1.4)
Ulcerative colitis	23 (56.1)	Collagenous colitis	2 (1.4)
Crohn's disease	13 (31.7)	Indeterminate colitis	1 (0.7)
Indeterminate IBD	6 (14.6)	Anatomical dysfunction	1 (0.7)
		Diarrhea after coronavirus	1 (0.7)

*Some of the patients have more than one cause.

n: number, %: percent, IBD: Inflammatory bowel diseases.

Supplementary Table 1. Change of laboratory parameters according to diarrhea causes[a]

	Infectious causes n (%)	Inflammatory bowel diseases n (%)	Irritable bowel syndrome n (%)	Others * n (%)	p value
Leukocytosis (n=143)	11 (17.7)	10 (25.0)	1 (4.8)	1 (5.0)	0.11
Leukopenia (n=143)	2 (3.2)	1 (2.5)	-	2 (10.0)	0.41
Elevated CRP (n=122)	24 (44.4)	26 (70.3)	1 (6.3)	8 (53.3)	<0.001
Elevated ESR (n=58)	6 (33.3)	10 (41.7)	-	2 (25.0)	0.17
Elevated transaminase levels (n=143)	5 (8.1)	1 (2.5)	1 (4.8)	1 (5.0)	0.78
Elevated LDH (n=110)	9 (18.8)	4 (12.9)	2 (12.5)	2 (13.3)	0.90

[a]Numbers and percentages belong to columns. *Others: Celiac disease, malignancy, drug-related diarrhea, adenoma/polyp, chronic pancreatic insufficiency, collagenous colitis, indeterminate colitis, anatomical dysfunction, and prolonged diarrhea after coronavirus.

n: number, %: percent, CRP: CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase.

in the remaining 39 (20.9%) patients. The cause of diarrhea was considered to be infectious in 66 (44.6%) patients [demonstrated by diagnostic methods in 22 (14.9%) patients - CMV positive patients were not included in this group because they did not have colonoscopic findings]; IBD in 41 (27.7%) patients and IBS in 22 (14.9%) patients. Celiac disease, malignancy, drug-related diarrhea, adenoma/polyp, chronic pancreatic insufficiency, collagenous colitis, indeterminate colitis, anatomical dysfunction, and prolonged diarrhea after coronavirus were detected less frequently or accompanying other diagnoses. The causes of diarrhea was presented in Table 2.

The laboratory results of the patients were evaluated according to the causes of diarrhea, and no difference was found in leukocytosis, leukopenia, ESR, transaminase and LDH values. There was only difference in CRP values ($p<0.001$). When subgroup analyzes were made, it was seen that this difference was due to the low CRP values in IBS patients. The variation of laboratory parameters according to the causes of diarrhea was presented in Supplementary Table 1.

Treatment was given to 113 (60.0%) of the patients presenting with diarrhea, and anti-infectives were included in the prescriptions written to 72 (63.7%) patients. Anti-infective preferences were given to the patients were ciprofloxacin and metronidazole in 30 (41.66%) patients; only metronidazole in 25 (34.7%) patients; only ciprofloxacin in 5 (6.9%) patients; amoxicillin-clavulanic acid and clarithromycin in 3 (4.2%) patients; tetracycline and metronidazole in 3 (4.2%) patients and rifaximin in 2 (2.8%) patients, respectively. There were 1 (1.4%) patient each given albendazole, ciprofloxacin and ornidazole, rifaximin and ornidazole, and nifuroxazide. Except for anti-infective drug, mesalazine in 35 (30.9%) patients; steroid in 14 (12.4%) patients; azathioprine was preferred in 9 (7.9%) patients, respectively. Symptomatic treatments were used in the remaining patients.

DISCUSSION

Acute and persistent diarrhea occur more frequently due to infectious causes and are more common in low- and middle-income countries where sanitation is inadequate [1]. Chronic diarrhea, on the other hand, is distinguished from others by its duration. Patients with chronic diarrhea usually require additional investigations, but in some, the history and physical examination may be sufficient to guide treatment. For example, diet, medications, surgery, radiation therapy, and IBS can be distinguished from the patients' history. Testing may be required when alarm symptoms are present (eg, weight loss, bloody stool), when there is no obvious cause, or for differential diagnosis [2]. In our study, patients who applied to the gastroenterology outpatient clinic with diarrhea were evaluated. The applications with chronic diarrhea were higher as expected (121 patients, 64.7%). Considering that patients with acute or persistent diarrhea often apply to infectious diseases, family medicine and internal medicine clinics or emergency department, the rate of acute or persistent diarrhea in 35.3% of the patients presenting to the gastroenterology clinic can be considered high.

A concomitant disease was observed in 16 (50%) patients who presented with acute diarrhea. While self-limiting acute diarrhea in adults usually does not require hospital admissions [1,9], the high rate in our study can be explained by the fact that patients behave cautiously and apply to hospitals more frequently in the presence of concomitant disease.

The cause of diarrhea was detected in 73.6% of the patients with chronic diarrhea, 87.5% of the patients with acute diarrhea, and 91.2% of the patients with persistent diarrhea. The difference may be due to not evaluating all causes and investigate accordingly in chronic diarrhea in which less common causes can be seen [3]. Bile acid and carbohydrate malabsorption, chronic idiopathic secretory diarrhea, fecal incontinence, functional and iatrogenic diarrhea, autonomic neuropathy, peptide-secreting tumors, immunodeficiencies, microscopic colitis, amyloidosis, dermatological and endocrinological diseases should be considered in selected patients and investigation should be performed accordingly [2].

In 39 (20.9%) of the patients, the cause of the diarrhea could not be determined. Insufficient history taking (eg, intolerance to specific nutrients, diet, alcohol use, history of surgery, presence of radiotherapy, family history etc.), physical examination, inadequate use of diagnostic methods (eg, electrolyte search in stool, evaluation of stool composition, lack of pathological examination of the colon mucosa etc.) or patients' non-compliance with the requested examinations (eg, refusal of colonoscopic evaluation etc.) were observed as the causes of undiagnosed cases.

Although an infectious cause (bacteria, protozoa and/or virus) was detected in 12.8% of 108 patients, anti-infective drugs were used in 38.5% of the patients. The rate of anti-infective use in acute and persistent diarrhea is 62.5%. Although an infectious causes were shown only in 8.3% of 121 patients with chronic diarrhea, anti-infective treatments were used in 31.4% of the patients. This situation can be expected considering acute and persistent diarrhea in Turkey. However, it can be clearly observed that anti-infective drug use is significantly high in patients with chronic diarrhea. Mostly prescribed anti-infective agents for chronic diarrhea were metronidazole in 75.0% (24 out of 32 prescriptions) and ciprofloxacin in 37.5% (12 out of 32 prescriptions). Although the high rate of metronidazole use is thought to be stemmed from possibility of a chronic infection, these high rates of ciprofloxacin treatment could not be attributed to a rational reason. In two different guidelines, which compiled the causes of chronic diarrhea, it was stated that chronic diarrhea of infectious origin is a rare condition in developed countries, but anti-infective use is appropriate in cases where the agent is indicated [10,11]. Among the reasons for high rates of anti-infective use, physicians' tendency to prescribe anti-infective agents even in the absence of an evidence of infection in patients with acute or persistent diarrhea [1,7]. This situation can be attributed to the fact that Turkey is a developing country and physicians may want to rule out infectious causes in the differential diagnosis process by prescribing anti-infective agents. However, this situation not only causes inappropriate anti-infective use, but also leads to drug-related side effects and increased drug resistance.

In patients who cannot be diagnosed with anamnesis and physical examination, it was observed that requesting full blood count, LDH, ESR, and transaminases did not make an additional contribution to the diagnosis. Only the CRP value might be helpful in the differential diagnosis of IBS in which CRP values were within normal levels in 93.7% of the patients [12,13]. While laboratory testing is not needed in most of the patients presenting with acute diarrhea, the type of the laboratory test should be selected in accordance with the patient history and clinical presentation in persistent and chronic diarrhea, and the habit of ordering unnecessary laboratory tests for each patient should be avoided as much as possible.

There were some limitations in the presented study. Firstly, there were data deficiencies due to the retrospective nature of the study. Secondly, the study employed a small number of patients, and therefore generalizability of its results to national level could not possible. Lastly, viral agents other than rotavirus were not investigated.

Chronic diarrhea is among the frequent reasons for admission to gastroenterology clinics, but acute or persistent diarrhea is also frequently among the reasons for outpatient referral. Although the cause of diarrhea was found in most of the patients presenting with diarrhea, the cause could not be determined in some patients at the time of admission. Prescribing anti-infectives should be avoided as much as possible in patients whose infectious cause cannot be determined. All differential diagnoses should be screened patiently with anamnesis, physical examination, imaging, appropriate stool and blood tests. When such an approach is taken, the number of patients whose cause of diarrhea cannot be found would gradually decrease.

Although diarrhea is a common health problem that affects many regions around the world, studies comparing acute, persistent and chronic diarrhea and evaluating patients' demographic, clinical, laboratory, imaging and biopsy results, and treatments and responses are relatively few. There is a need for detailed and extensive research in this area.

Author contribution

Study conception and design: ÇMA, BB, and EK; data collection: ÇMA and BB; analysis and interpretation of results: ÇMA and BB; draft manuscript preparation: ÇMA, BB, and EK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ankara City Hospital Clinical Research Ethics Committee (Protocol no. 20-1344/06.01.2021).

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Conflict of interest

The authors declare that there is no conflict of interest.

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