Diagnostic Performance of Esophagogastroduodenoscopy, Colonoscopy, and Small Bowel Endoscopy in Thai Adults with Chronic Diarrhea

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Research Article

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Abstract

Background: Gastrointestinal endoscopy is recommended to investigate chronic diarrhea in Western countries, but its benefits have infrequently been investigated in Southeast Asia. This study aimed to determine the diagnostic utility of esophagogastroduodenoscopy (EGD), colonoscopy, and small bowel endoscopy in Thai chronic diarrhea.

Methods: Medical records of consecutive patients who underwent EGD and/or colonoscopy to investigate chronic diarrhea at our center from 2008 to 2012 were reviewed. We also evaluated consecutive patients with negative EGD and colonoscopy who underwent subsequent small bowel endoscopy, including push enteroscopy, balloon-assisted enteroscopy (BAE), and video capsule endoscopy (VCE), from 2008 to 2018. The diagnostic yield of each endoscopic modality was analyzed.

Results: A total of 272 patients underwent EGD and/or colonoscopy. Mean hemoglobin and albumin levels were 11.6 g/dL and 3.8 g/dL, respectively. EGD and colonoscopy were performed in 135 and 269 patients, respectively, and the diagnostic yield was 5.9% for EGD and 42.7% for colonoscopy. No patient with normal colonoscopy had positive EGD findings. Thirty-nine patients with normal EGD and colonoscopy underwent small bowel endoscopy. Mean hemoglobin and albumin levels were 10.9 and 2.7 g/dL, respectively. Push enteroscopy, BAE, and VCE were performed in 22, 20, and 11 patients with a diagnostic yield of 22.7%, 60.0%, and 45.5%, respectively.

Conclusion: Colonoscopy was shown to be an essential investigation in chronic diarrhea. In contrast to western, EGD did not add benefit to colonoscopy. Enteroscopy played an important role in the diagnosis of chronic diarrhea when colonoscopy was negative.

Introduction

Diarrhea is defined by abnormal stool weight (> 200 g/day) or frequency (> 3 times/day). Four-week symptom duration is generally considered to be the cutoff for distinguishing acute from chronic diarrhea.[1, 2] Chronic diarrhea was estimated to affect approximately 5% of the Western population.[1] Functional disorder (e.g., irritable bowel syndrome [IBS]) and inflammatory diseases (e.g., inflammatory bowel disease [IBD], microscopic colitis, and celiac disease) are the most common causes of chronic diarrhea in western countries.[3, 4] In addition to taking a detailed history and performing a complete physical examination, endoscopic evaluation should be considered in patients with inconclusive diagnosis after routine blood and stool tests or who fail to respond to empirical therapy.

According to the American Society for Gastrointestinal Endoscopy guidelines, a diagnostic colonoscopy should be performed to evaluate chronic diarrhea.[5] The diagnostic yield of colonoscopy in patients with chronic diarrhea ranges from 18–31% in Western countries, and the common diagnoses are IBD or microscopic colitis.[3, 4, 6] Upper gastrointestinal (GI) evaluation for diseases involving the duodenum should also be considered in patients with chronic diarrhea that have negative findings on lower

endoscopy.[5] Celiac disease, giardia infection, Crohn's disease, eosinophilic gastroenteritis, Whipple's disease, and intestinal amyloid are probable diagnoses in these patients.[5] Among patients with normal esophagogastroduodenoscopy (EGD) and colonoscopy, video capsule endoscopy (VCE) was reported to have a diagnostic yield ranging from 43–54%.[7, 8] Deep enteroscopy, which can obtain tissue samples, demonstrated potential for diagnosing small bowel disease in patients presenting with chronic diarrhea[9–13], but data are limited.

Although gastrointestinal endoscopy is recommended to investigate chronic diarrhea in Western countries, its benefits have infrequently been investigated in Southeast Asia. Moreover and importantly, the etiologies of chronic diarrhea in Southeast Asia differ from those in Western countries. Southeast Asia has a higher prevalence of gastrointestinal infections but a lower prevalence of celiac and IBD. Accordingly, the aim of this study was to investigate the diagnostic utility of esophagogastroduodenoscopy (EGD), colonoscopy, and small bowel endoscopy in Thai adults with chronic diarrhea.

Materials And Methods

Study design and population

We retrospectively reviewed the medical records of consecutive patients aged 18 years or older who underwent EGD and/or colonoscopy to investigate chronic diarrhea at Siriraj Hospital, Bangkok, Thailand, from January 2008 to December 2012. We also evaluated consecutive patients with negative EGD and colonoscopy who underwent subsequent small bowel endoscopy, including push enteroscopy, balloon-assisted enteroscopy (BAE), and video capsule endoscopy (VCE), from January 2018 to December 2018. We excluded patients with a personal history of underlying intestinal conditions, such as IBD or short bowel syndrome. All methods were carried out in accordance with the Declaration of Helsinki. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) on 17 January 2019 (COA no. 045/2019). The requirement to obtain written informed consent from included patients was waived by the Siriraj Institutional Review Board due to the anonymous retrospective nature of this study.

Definitions and collected data

In this study, the definition of chronic diarrhea was watery stool ≥ 3 times/day or ≥ 1 occurrence of mucous-bloody stool per day for more than four weeks. Patient demographic data, clinical presentations, blood and stool tests, endoscopic findings, pathological findings, and radiological findings were reviewed from electronic medical records. Definite diagnoses were made based on the findings of specific investigations that were ordered based on suspicion of a specific disease and response to therapy. The diagnostic yield of each endoscopic modality was calculated. Furthermore, since small bowel endoscopy is invasive and not widely available, a decision to perform small bowel endoscopy should be carefully made. Therefore, we evaluated predictive factors for small bowel mucosal diseases in patients with

negative EGD and colonoscopy who underwent small bowel endoscopy in which diagnostic endoscopy would be of benefit.

Since this was a retrospective observational study, patient characteristics between those who underwent EGD and/or colonoscopy and those with negative EGD and colonoscopy who underwent small bowel endoscopy were different. As such, the EGD and/or colonoscopy patients and the small bowel endoscopy patients were analyzed separately.

Statistical methods

Continuous data are presented as mean and standard deviation if normally distributed, and as median and range or interquartile range (IQR) if not normally distributed. Categorical variables are presented as frequency and percentage. We assessed the diagnostic yield of each endoscopic modality. Comparison of the diagnostic performance of EGD to colonoscopy, and colonoscopy to colonoscopy without ileal intubation was performed using McNemar's test. Analysis to identify independent predictors of small bowel mucosal diseases in patients with negative EGD and colonoscopy who underwent small bowel endoscopy was performed based on logistic regression. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS Statistics software (SAS, Inc., Cary, NC, USA).

Results

Diagnostic performance of EGD and colonoscopy

A total of 272 consecutive patients who underwent EGD and/or colonoscopy to investigate chronic diarrhea were included in this analysis. Baseline characteristics are outlined in Table 1. The mean age was 54 years, and 111 (40.8%) patients were male. The mean hemoglobin and albumin levels were 11.54 g/dL and 3.76 g/dL, respectively. The median duration of symptoms at presentation was 12 weeks. Of 272 patients, 132 underwent both EGD and colonoscopy, 137 underwent only colonoscopy, and 3 underwent only EGD (Figure 1). A diagnosis was obtained from endoscopy for 116 of 272 (42.6%) patients. The definite diagnoses are shown in Table 1. Among the 269 patients who underwent colonoscopy, 115 (42.7%) obtained a definite diagnosis. Isolated ileal involvement without colonic lesions was found in 9 patients. Among the 135 patients who underwent EGD, 8 (5.9%) patients obtained a definite diagnosis, including two gastrointestinal lymphoma, and one each for all of the following: Peutz-Jeghers syndrome, Non-steroidal anti-inflammatory drug (NSAID)-induced enteropathy, cytomegalovirus (CMV) infection, eosinophilic enteritis, graft-versus-host disease, and systemic mastocytosis. All patients whose EGD found positive findings also had abnormal colonoscopic findings except for one with lymphoma who underwent only EGD. No patients with normal colonoscopy had abnormal EGD findings. Among 132 patients who underwent both EGD and colonoscopy, colonoscopy made a definite diagnosis in 50 (37.9%) patients, which is significantly higher than the 7 (5.3%) diagnoses made by EGD (p<0.001), and higher than colonoscopy if ileal intubation had not been performed, which could make a definite diagnosis in 44 (33.3%) patients (p=0.03).

Table 1

Characteristics of consecutive patients who underwent EGD and/or colonoscopy (N=272)

Characteristics	Total
Age (years), mean±SD	54.03±15.00
Male gender, n (%)	111 (40.8%)
Body mass index (kg/m^2), mean±SD	21.54±4.50
Comorbidity, n (%)	
· Diabetes mellitus	47 (17.3%)
· Kidney disease	14 (5.2%)
· Liver disease	29 (10.6%)
· Human immunodeficiency virus	19 (7.0%)
· Immunosuppressive agents	23 (8.5%)
Presentation, n (%)	
· Duration of symptoms (weeks), median (IQR)	12 (4.5-24)
· Diarrhea characters	
o Watery	199 (73.2%)
o Bloody	77 (28.3%)
o Steatorrhea	1 (0.4%)
· Abdominal pain	123 (45.2%)
· Fever	31 (11.4%)
· Weight loss	172 (63.2%)
· Edema	31 (11.4%)
Investigations	
· Hemoglobin (g/dL), mean±SD	11.54±2.23
· Albumin (g/dL), mean±SD	3.76±2.23
· Number of stool tests (median, IQR)	2 (0.5-3)
· Stool fat (n=44), n (%)	10 (21.7%)
Definite diagnosis made by EGD and/or colonoscopy	(n=116)
Infections, n (%)	30 (25.9%)
· Tuberculosis	9 (7.8%)
· Cytomegalovirus colitis	6 (5.2%)

· Parasite or protozoa	5 (4.3%)
· Presumed Clostridium difficile infection*	7 (6.0%)
· Self-limiting colitis	3 (2.6%)
Malignancies, n (%)	21 (18.1%)
· Colon cancer	16 (13.8%)
· Lymphoma	5 (4.3%)
Inflammatory bowel disease, n (%)	29 (25.0%)
· Crohn's disease	9 (7.8%)
· Ulcerative colitis	20 (17.2%)
Eosinophilic colitis, n (%)	13 (11.2%)
Radiation proctocolitis, n (%)	6 (5.2%)
Non-steroidal anti-inflammatory drug-induced colitis, n (%)	5 (4.3%)
Ischemic colitis, n (%)	3 (2.6%)
Microscopic colitis, n (%)	3 (2.6%)
Others, n (%)	6 (5.2%)
Abbreviations: EGD, esophagogastroduodenoscopy; SD, standard deviation; IQR, interquartile range *Presumed Clostridium difficile infection was defined as endoscopic findings of pseudomembranous colitis with response to metronidazole or oral vancomycin	

Diagnostic performance of small bowel endoscopy and small bowel imaging

Thirty-nine consecutive patients with negative EGD and colonoscopy findings undergoing small bowel endoscopy were included. Baseline characteristics are demonstrated in Table 2. The mean age was 47 years, and 20 (51.3%) patients were male. The median duration of symptoms prior to presentation was 24 weeks (IQR: 8-48). The mean hemoglobin and albumin levels were 10.92 and 2.70 g/dL, respectively. Push enteroscopy, BAE, and VCE were performed in 22, 20, and 11 patients, respectively. As shown in Table 2, nineteen patients had mucosal diseases. All of those patients were diagnosed by small bowel endoscopy, except one patient with intestinal capillariasis who was diagnosed by repeated stool examination after negative push enteroscopy. Twenty patients had non-mucosal diseases.

As shown in Figure 2, the diagnostic yield of push enteroscopy, BAE, and VCE was 22.7% (5/22), 60.0% (12/20), and 45.5% (5/11), respectively. For 17 patients with negative PE, 3 had mucosal diseases missed

by PE, including 2 intestinal capillariasis and 1 small bowel Crohn's disease. Of these three, two were diagnosed by subsequent BAE, and the other one was diagnosed by repeated stool examination. For 8 patients with negative BAE, only one had a mucosal disease. This patient was diagnosed by typical VCE finding and response to anti-parasitic agents. Small bowel imaging, either small bowel follow-through (SBFT) or computed tomography (CT) abdomen, was performed before enteroscopy in 6 of 22 push enteroscopy, and in 17 of 20 balloon-assisted enteroscopy. Among the procedures that had abnormal small bowel imaging performed prior to the procedure, the diagnostic yield was 63.2% (12 of 19). The diagnostic yield was 21.1% (4 of 19) and 25.0% (1 of 4) in the procedures without small bowel imaging and in the procedures with normal small bowel imaging, respectively.

Concerning VCE, as shown in Figure 2, 3 of 11 patients underwent VCE first. Two of those three patients had positive findings, and those two patients subsequently underwent BAE and obtained a definite diagnose. Seven of 11 VCE were performed after small bowel enteroscopy, and 5 of 7 were performed after negative results of small bowel enteroscopy. VCE detected an abnormality in one patient that led to a diagnosis of parasitic infection, and VCE confirmed the diagnosis of non-mucosal disease in 4 patients. The remaining 2 of 7 patients underwent VCE to evaluate disease extension after enteroscopy detected abnormal findings. The last patient underwent only VCE and had negative findings. Among the six patients with negative VCE findings, none had the mucosal disease.

Table 2

Characteristics of consecutive patients who underwent small bowel endoscopy and their final diagnoses

Characteristics	Total (n=39)
Age (years), mean±SD	47.03±11.98
Male gender, n (%)	20 (51.3%)
Body mass index (kg/m2), mean±SD	19.26±4.24
Comorbidity, n (%)	
· Diabetes mellitus	9 (23.1%)
· Kidney disease	3 (7.7%)
· Liver disease	5 (12.8%)
· Human immunodeficiency virus	3 (7.7%)
· Immunosuppressive agents	6 (15.4%)
Presentation, n (%)	
· Duration (weeks), median (IQR)	24 (8-48)
· Diarrhea characters	
o Watery	37 (94.9%)
o Bloody	6 (15.4%)
o Steatorrhea	3 (7.7%)
· Abdominal pain	17 (43.6%)
· Fever	2 (5.1%)
· Weight loss	34 (87.2%)
· Edema	15 (38.5%)
Investigations	
· Hemoglobin (g/dL), mean±SD	10.92±2.17
· Albumin (g/dL), mean±SD	2.70±1.19
· Stool fat (n=29), n (%)	9 (31.1%)
Final diagnoses	
Mucosal diseases, n (%)	(n=19)
Capillariasis	6 (31.6%)

Isospora belli	2 (10.5%)
Cytomegalovirus	1 (5.3%)
Gastrointestinal lymphoma	1 (5.3%)
Crohn's disease	2 (10.5%)
Eosinophilic enteritis	2 (10.5%)
NSAID-induced colitis	1 (5.3%)
SLE vasculitis	2 (10.5%)
Idiopathic enteritis	2 (10.5%)
Non-mucosal diseases, n (%)	(n=20)
Irritable bowel syndrome	4 (20.0%)
Small intestinal bacterial overgrowth	6 (30.0%)
Pancreatic diseases	2 (10.0%)
Diabetic diarrhea	2 (10.0%)
Adrenal insufficiency	1 (5.0%)
Drug-induced diarrhea	2 (10.0%)
SLE protein losing enteropathy	3 (15.0%)
Abbreviations: SD, standard deviation; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SLE, system lupus erythematosus	

Table 3 shows univariate and multivariate analysis to identify factors that independently predicted small bowel mucosal diseases. Younger age and lower albumin levels were found to be significant predictors of mucosal disease in univariate analysis. Although multivariate analysis revealed no independent predictive factors, a trend towards independent prediction was found for lower albumin levels with an odds ratio of 0.52 (95% confidence interval: 0.25-1.08; p=0.08).

Table 3

Univariate and multivariate analysis to identify factors that independently predict mucosal disease

Factors	Univariate analysis	p-value	Multivariate analysis	p-value
	Odds ratio (95%CI)		Odds ratio (95% CI)	
Age	0.94 (0.88-0.99)	0.046	0.96 (0.90-1.03)	0.290
Male gender	2.57 (0.71-9.36)	0.152		
Body mass index	0.90 (0.76-1.05)	0.184		
Bloody stool	6.78 (0.71-64.70)	0.096	4.69 (0.37-59.10)	0.232
Steatorrhea	0.50 (0.04-6.02)	0.585		
Abdominal pain	3.21 (0.86-12.02)	0.084	1.20 (0.22-6.43)	0.828
Fever	1.06 (0.06-18.17)	0.970		
Weight loss	4.50 (0.46-44.54)	0.198		
Edema	2.27 (0.86-6.00)	0.098		
Hemoglobin levels	1.17 (0.86-1.59)	0.313		
Albumin levels	0.49 (0.26-0.92)	0.025	0.52 (0.25-1.08)	0.08
A p-value<0.05 indicates statistical significance Abbreviation: CI, confidence interval				

Discussion

In this study, we found the etiologies of chronic diarrhea in Thai patients to be different from those in Western patients, particularly in small bowel diseases. Among chronic diarrhea with ileocolonic causes, the common causes in our cohort were infectious diseases and inflammatory bowel diseases, whereas IBD and microscopic colitis are the common causes in Western countries. In small bowel diseases, the most common cause of chronic diarrhea in our cohort was parasitic infections. Interestingly, we found no celiac disease, which is the common cause of small bowel disease in Western countries.

Similar to Western countries, our study showed that colonoscopy had high diagnostic performance in patients with chronic diarrhea. The diagnostic yield was 42.7%, which is comparable to the values reported by several previous studies (range: 10.0% to 49.5%).[3, 14-17] Furthermore, our study showed that the terminal ileum should be accessed because the diagnostic yield would have been decreased from 42.7% to 39.4% if the terminal ileum had not been intubated. Makkar, *et al.* reported that the diagnostic

yield was 15.0% when colonoscopy was performed without ileal intubation, and the yield increased to 16.9% when performed with ileoscopy.[18]

American Society for Gastrointestinal Endoscopy guideline recommends EGD for chronic diarrhea work-up due to its potential for diagnosing celiac disease.[5, 19] However, the prevalence of celiac disease is low in Southeast Asia[20]; therefore, EGD had a diagnostic yield of only 5.9% in this study. Furthermore, all positive findings were also detected if ileocolonoscopy was performed, which means that EGD conferred no additional diagnostic benefit when combined with colonoscopy. This finding suggests that EGD should not be routinely performed to investigate chronic diarrhea in our region.

Interestingly, the involved small bowel segments causing chronic diarrhea in our cohort were at more distal segments that are unreachable by EGD. Nineteen patients with negative EGD and colonoscopy who underwent small bowel endoscopy were found to have mucosal diseases. Of those, 5 were diagnosed by push enteroscopy, 12 by balloon-assisted enteroscopy, 1 by typical VCE finding of intestinal capillariasis, and 1 by repeated stool examination. The diagnostic yield of push enteroscopy, BAE, and VCE was 22.7%, 60.0%, and 45.5%, respectively. Push enteroscopy could be considered instead of EGD when diarrhea from small bowel lesions is suspected in our region despite having the lowest diagnostic yield among the three modalities since most general gastroenterologists can perform it, and it is less invasive and less expensive than BAE. Balloon-assisted enteroscopy, which can more deeply access the small bowel compared to push enteroscopy, was reported the have a diagnostic yield of 55.0% to 73.5% in previous studies.[10-13] Similarly, the diagnostic yield of BAE in our study was 60%. It is essential to note that small bowel imaging studies could contribute to the high diagnostic yield of BAE since 17 of 20 BAE had small bowel imaging performed before BAE to localize the lesions. Furthermore, in 12 patients whose diagnoses were obtained by BAE, almost all (11 of 12) had lesion localization by small bowel imaging studies before the endoscopy. For VCE, the diagnostic yield in this study was 45%, which is comparable to previous studies.[7, 8] The major limitation of VCE is its inability to obtain tissue sampling. However, our study showed that VCE could help to guide the abnormal findings prior to BAE and exclude small bowel mucosal lesions if the results were normal.

Our study showed that small bowel imaging studies, either SBFT or CT abdomen, should be considered as a supplementary investigation to localize the lesion and guide which endoscopic modality should be performed. The diagnostic yield of small bowel enteroscopy was higher if those procedures were performed with guidance from small bowel imaging. As mentioned above, 11 of 12 positive BAE had lesions localization by small bowel imaging studies. Furthermore, a normal imaging study result could suggest non-mucosal diseases; only one of 4 patients with normal imaging had a mucosal disease.

For the predictive factors associated with the diagnosis of small bowel mucosal diseases among patients with negative EGD and colonoscopy, lower albumin level was the significant predictor in univariate analysis, and it was almost significant in multivariate analysis. This result is in accordant with the study by Song *et al*., which showed that hypoalbuminemia and hematochezia were significant predictive factors for a positive diagnostic yield of VCE in patients with chronic diarrhea.[7]

Based on the results of this study, we propose a diagnostic diagram for patients with chronic diarrhea in our region, as shown in Figure 3.

Strengths and limitations

The strength of this study is that it is the first to report the diagnostic performance of each endoscopic modality in chronic diarrhea in an area with a high prevalence of infections and a low prevalence of celiac disease. We also investigated the role of small bowel imaging in the diagnosis of chronic diarrhea. The most notable limitation is our study's retrospective design, which made it impossible to perform all evaluated modalities in all patients. Another limitation is that our data were collected from a single center.

Conclusion

In Thailand, colonoscopy is the mainstay investigation in patients with chronic diarrhea. EGD was found to have a low diagnostic yield, and it did not show added benefit when combined with colonoscopy because most of the small bowel lesions were in the jejunum and ileum, which are unreachable by EGD. Enteroscopy, which has more potential for reaching the abnormal small bowel segments than EGD, should be considered, particularly in patients with significant hypoalbuminemia. Small bowel imaging studies or VCE should be able to guide the endoscopic route and might support non-mucosal diseases if the findings are normal.

Abbreviations

BAE Balloon-assisted enteroscopy

BMI Body mass index

CI Confidence interval

CMV Cytomegalovirus

COA Certificate of approval

CT Computed tomography

DM Diabetes mellitus

EGD Esophagogastroduodenoscopy

GI Gastrointestinal

Hb Hemoglobin

HIV Human immunodeficiency virus

IBD Inflammatory bowel disease

IBS Irritable bowel syndrome

IQR Interquartile range

NSAID Non-steroidal anti-inflammatory drug

SBFT Small bowel follow through

SLE Systemic lupus erythematosus

VCE Video capsule endoscopy

Declarations

Ethics approval and consent to participate

All methods were carried out in accordance with the Declaration of Helsinki. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) on 17 January 2019 (COA no. 045/2019). The requirement to obtain written informed consent from included patients was waived by the Siriraj Institutional Review Board due to the anonymous retrospective nature of this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to our center's patient confidentiality policies, but they may be made available by the corresponding author to appropriate parties upon reasonable request.

Conflict of interest declaration

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

Funding disclosure

This was an unfunded study.

Author's contributions

NP, PC, and JL conceived and designed the study. JL, CS, AP, PA, PP, and NS acquired the data. JL and NP analyzed and interpreted the data. JL and CS wrote the first draft of the manuscript. NP and PC critically reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

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Figures

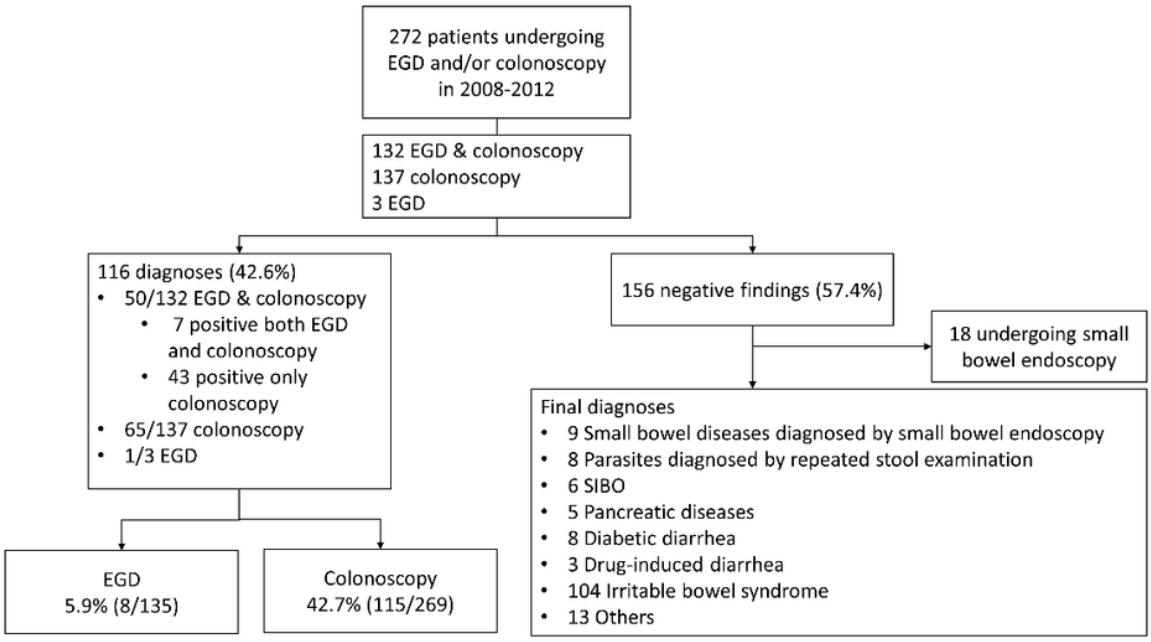

Figure 1

Diagnostic flow diagram in consecutive patients who underwent esophagogastroduodenoscopy and/or colonoscopy during 2008 to 2012 (Abbreviation: EGD, esophagogastroduodenoscopy)

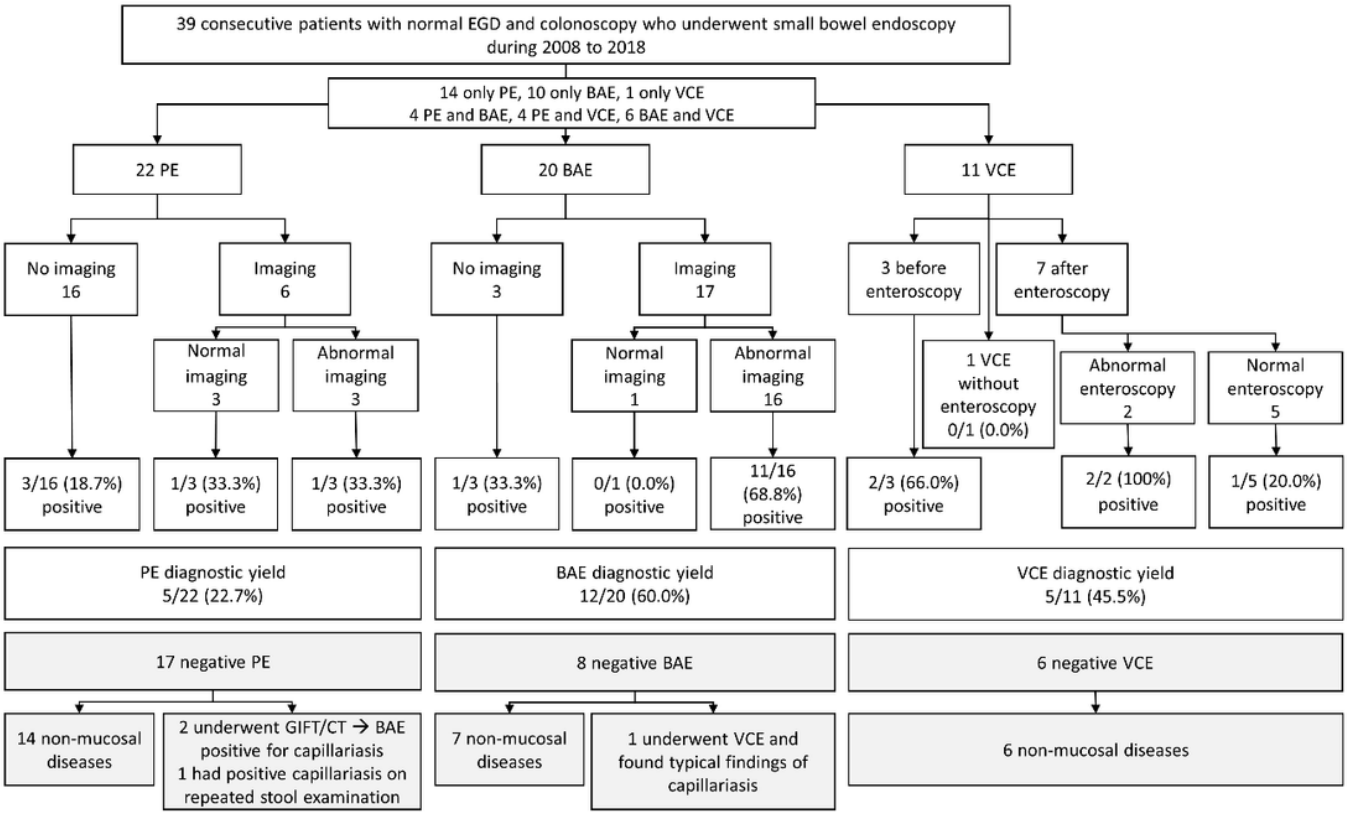

Figure 2

Diagnostic flow diagram of patients with negative esophagogastroduodenoscopy and colonoscopy and who underwent subsequent small bowel endoscopy (Abbreviations: EGD, esophagogastroduodenoscopy; PE, push enteroscopy; BAE, balloon-assisted enteroscopy; VCE, video capsule endoscopy)

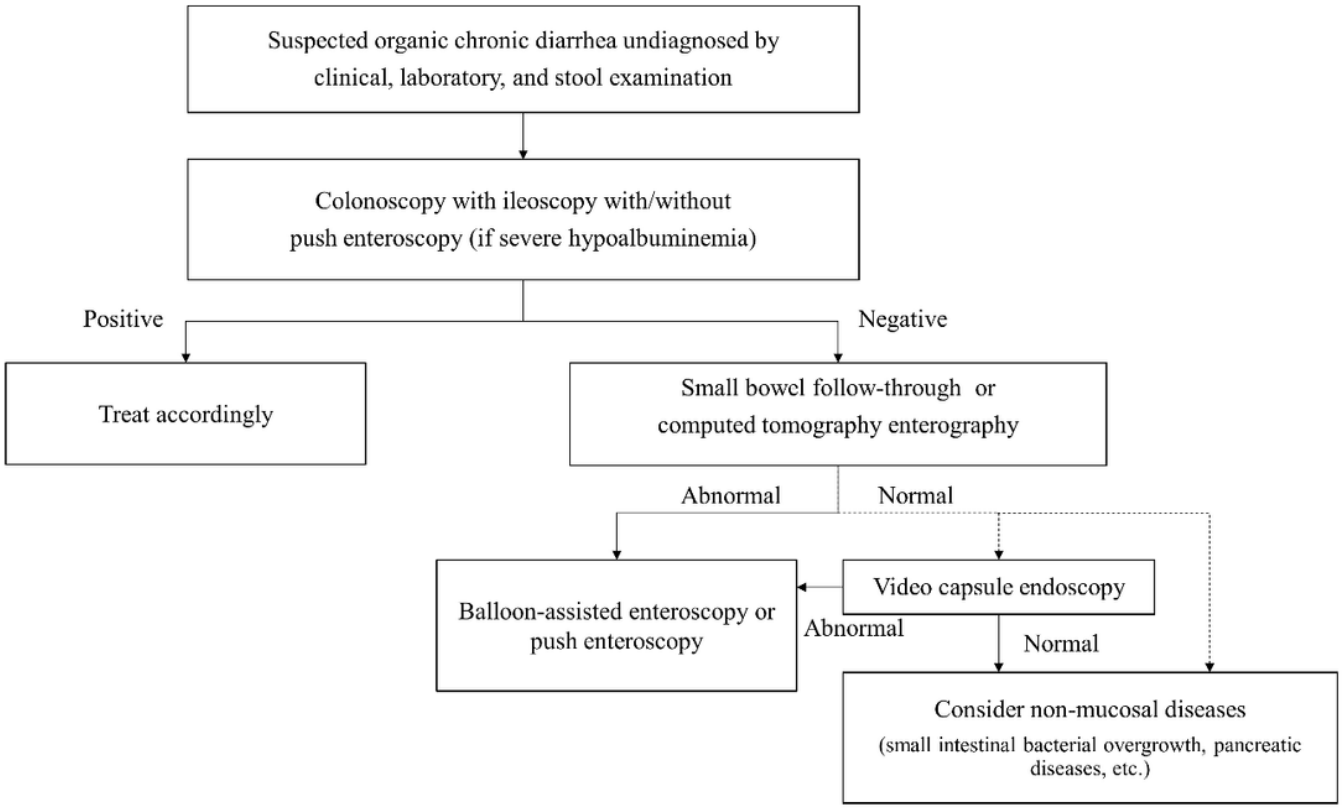

Figure 3

Proposed diagnostic algorithm for patients with chronic diarrhea