Annals of Gastroenterology (2026) **39,** 614-618

Is common variable immunodeficiency associated with diverticulitis? A matched cohort study

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Abstract

Background The aim of this study was to evaluate the likelihood of acute diverticulitis and its severity in patients with common variable immunodeficiency (CVID) compared to matched controls among those who presented to the emergency room and underwent computed tomography (CT) imaging for abdominal pain.

Methods This was a multicenter, retrospective study comparing adult patients with a diagnosis of CVID, who had CT imaging for abdominal pain between the years 2015-2024, to a control cohort of adult patients without CVID. Mann-Whitney *U* and chi-square tests were performed to compare baseline characteristics between cases and controls. Mantel-Haenszel tests and conditional logistic regression were used to evaluate associations between CVID, diverticulitis and selected variables.

Results A total of 1392 patients were included in the analysis (696 with CVID and 696 without CVID). Of these patients, 72% were female, 96% were white, their median age was 57 years, and their median body mass index was 27.8 kg/m^2. CVID was associated with lower odds of diverticulitis (odds ratio [OR] 0.41, 95% confidence interval 0.27-0.63; P<0.001). There was no difference between the rates of complicated diverticulitis. Among patients with CVID who were diagnosed with diverticulitis, 51.4% (vs. 45%, OR 1.27, 95%CI 0.57-2.81; P=0.563) required inpatient treatment, 22.9% required surgical intervention (vs. 16.5%, OR 1.50, 95%CI 1.50 (0.56-4.04); P=0.418), and 31.4% (vs. 24.1%, OR 1.45, 95%CI 0.60-3.49; P=0.411) had recurrent diverticulitis.

Conclusion Patients with CVID presenting to the emergency department have lower odds of acute diverticulitis among those who underwent CT imaging for abdominal pain.

Keywords Common variable immunodeficiency, diverticulitis, abdominal pain

Ann Gastroenterol 2026; 39 (5): 614-618

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Conflict of Interest: Asad Ur Rahman: Abbvie Inc Speaker Bureau

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Received 20 November 2025; accepted 27 January 2026; published online 26 June 2026

DOI: https://doi.org/10.20524/aog.2026.1084

Introduction

Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency in adults. Its prevalence varies across different populations and regions, ranging from 0.001-3 per 100,000 [1]. The clinical presentation is heterogeneous, with patients experiencing a range of infectious and non-infectious complications [2]. The most common gastrointestinal symptoms include diarrhea, malabsorption and weight loss. The most common gastrointestinal infections associated with CVID are *Giardia*, Norovirus, *Campylobacter* and Cytomegalovirus [3,4]. In addition, CVID is associated with intestinal inflammation, probably due to T-cell dysfunction [5], as a result of which it can present with several non-infectious gastrointestinal conditions, such as CVID-enteropathy, microscopic colitis, celiac disease, lymphocytic gastritis, pernicious anemia, acute graft-vs.-host disease, inflammatory bowel disease

(IBD) and small-bowel lymphoma [3,4,6]. Gut microbiota alteration is also observed in both CVID and IBD, which could explain the similar presentation and mucosal inflammation seen in both conditions [7]. However, one of the most common inflammatory diseases of the gastrointestinal tract, diverticulitis, which has been linked to changes in microbiome composition and function [8], has not been studied in relation to CVID. The incidence of acute diverticulitis is approximately 4% over a decade in patients with diverticulosis [9]. The incidence is higher among immunocompromised patients, and they are more likely to present with severe or complicated diverticulitis [10,11]. The aim of this study was to evaluate the likelihood of acute diverticulitis and its severity in patients with CVID presenting to the emergency room who underwent computed tomography (CT) imaging for abdominal pain, compared to matched controls without CVID presenting to the emergency room who underwent CT imaging for abdominal pain.

Patients and methods

We performed a retrospective observational multicenter study that included adult patients (age ≥18 years) from hospitals in the Cleveland Clinic Enterprise (Florida and Ohio), between the years of 2015-2024. This study was approved by the Cleveland Clinic institutional review board (No. 24-145). Patients presenting to the emergency room and undergoing computed tomography (CT) with indication of abdominal pain were selected for evaluation.

Data were gathered from the electronic health record. CVID was identified using International Classification of Diseases (ICD) codes (ICD-10 D83.9 and ICD-9 279.06). The case cohort included patients with CVID who had CT imaging done for abdominal pain, whereas the control group was comprised of patients without a diagnosis of CVID who had CT imaging done for abdominal pain. The presence of acute diverticulitis was confirmed only if supporting CT imaging findings were present, which is the gold standard for its diagnosis. The severity of diverticulitis was defined using the modified Hinchey classification (if 1b or greater, it was considered complicated) (Supplementary Table 1). Recurrent diverticulitis was defined as the occurrence of additional episodes of acute diverticulitis (as defined above) after resolution of the index episode (at least 6 weeks after the index episode). These groups were then exact matched in a 1:1 ratio based on the following variables: age (±3 years), body mass index [(BMI) ±1.5 kg/m^2], sex, race, tobacco use (ever/never), ulcerative colitis, Crohn's disease, colorectal cancer, current use of a nonsteroidal anti-inflammatory drug (NSAID), and current steroid use.

The primary outcome measure was comparing the odds of diverticulitis occurrence between cases and controls. The secondary outcome measures were comparative incidence of complicated diverticulitis, need for surgical intervention, recurrent diverticulitis, and the impact of intravenous immunoglobulin (IVIG) on outcomes.

Statistical analysis

Data were assessed for normality, and appropriate descriptive statistics—including frequencies with percentages and medians with interquartile ranges (IQR)—were computed for all variables. Mann-Whitney *U* and chi-square tests were performed to compare baseline characteristics between cases and controls. Mantel-Haenszel tests and conditional logistic regression were used to evaluate associations between CVID, diverticulitis and selected variables. Data were analyzed using SPSS Version 29 (IBM Corp., Armonk, NY, USA). All tests were 2-tailed, and a P-value <0.05 was used to determine significance.

Results

During the study period, the case cohort included 838 patients and the control cohort 25107 patients. After exact matching, 1392 patients were included in the analysis (696 each, cases and controls). The median age was 57 years, 72% were female and 96% were white (Caucasian ethnicity). The median BMI was 27.8 kg/m^2. Table 1 presents the baseline characteristics and shows homogeneity of 2 groups after exact matching. The incidence of diverticulitis was 4.61% (35/696) in patients with CVID and 11.35% (79/696) in patients without CVID (P<0.001). (Table 2)

Table 3 illustrates the association of diverticulitis with selected variables. CVID was associated with lower odds of acute diverticulitis (5.0% vs. 11.4%; odds ratio [OR] 0.41 95% confidence interval [CI] 0.27-0.63; P<0.001). No other

Table 1 Baseline characteristics (N=1392)

Variable	CVID (N=696) median (IQR) or n (%)	No CVID (N=696) median (IQR) or n (%)	P-value
Age (years)	59 (46-68)	59 (45-67)	0.898
BMI (kg/m^2)	27.8 (23.6-33.3)	27.6 (23.7-33.1)	0.890
Female sex	506 (72.7)	506 (72.7)	>0.99
Race			>0.99
White	669 (96.1)	669 (96.1)	
Black	19 (2.7)	19 (2.7)	
Multiracial/ multicultural	8 (1.1)	8 (1.1)	
Current or past tobacco user	309 (44.4)	309 (44.4)	>0.99
Ulcerative colitis	11 (1.6)	11 (1.6)	>0.99
Crohn's disease	11 (1.6)	11 (1.6)	>0.99
Colorectal cancer	7 (1.0)	7 (1.0)	>0.99
NSAID user	183 (26.3)	183 (26.3)	>0.99
Steroid user	261 (37.5)	261 (37.5)	>0.99

CVID, common variable immunodeficiency; IQR, interquartile range; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug

variables (diabetes, hypertension, chronic kidney disease, heart failure, cirrhosis, chronic obstructive pulmonary disease/asthma, and alcohol use) were significantly associated with diverticulitis.

Table 4 shows the association between CVID and severity of diverticulitis, the need for surgical intervention, and recurrence of diverticulitis. The odds of complicated diverticulitis were comparable in both groups (20% vs. 21.5%, OR 0.91, 95%CI 0.34-2.45; P=0.854). A higher percentage of patients with CVID required surgical intervention (22.9% vs. 16.5%, OR 1.5, 95%CI 0.56-4.04; P=0.418) and developed recurrent diverticulitis (31.4% vs. 24.1%, OR 1.45, 95%CI 0.60-3.49; P=0.411). However, these findings did not reach statistical significance.

Table 5 shows the association between IVIG and diverticulitis among patients with CVID. The patients who received IVIG had lower odds of having complicated diverticulitis (11.1% vs. 29.5%, OR 0.30, 95%CI 0.05-1.82; P=0.228) or recurrent diverticulitis (22.2% vs. 41.2%, OR 0.41, 95%CI 0.09-1.78; P=0.289), but these differences did not reach statistical significance.

Among patients with CVID who presented with complicated diverticulitis, 3 patients had a perforation, 2 presented with an associated abscess, and 2 patients had fistulization into surrounding organs. In comparison, among patients without CVID who presented with complicated diverticulitis, 8 patients had a perforation, 7 had an abscess,

Table 2 Diverticulitis incidence in patients with and without CVID

	Diverticulitis n (%)	No diverticulitis n (%)	Total
CVID	35 (4.6)	661 (95.4)	696 (100)
No CVID	79 (11.4)	617 (88.6)	696 (100)
Total	114 (8.2)	1,278 (91.8)	1,392 (100)

OR, odds ratio; CI, confidence interval; CVID, common variable immunodeficiency
Odds ratio (CVID vs. no CVID): OR 0.41 (95%CI 0.27-0.63)

Table 3 Associations between diverticulitis and selected variables (N=1392)

Variable	Diverticulitis (N=114) n	No diverticulitis (N=1278) n	OR (95%CI)	P-value
CVID	35	661	0.41 (0.27-0.63)	<0.001
Diabetes	34	330	1.10 (0.61-1.98)	0.763
Hypertension	89	676	1.50 (0.80-2.82)	0.209
Chronic kidney disease	25	275	0.75 (0.38-1.47)	0.400
Cirrhosis	3	63	0.60 (0.14-2.51)	0.484
Heart failure	12	184	0.50 (0.23-1.07)	0.074
COPD/asthma	58	547	0.83 (0.48-1.42)	0.493
Current alcohol user	53	537	1.27 (0.75-2.12)	0.363

CVID, common variable immunodeficiency; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease

Table 4 Associations between CVID and diverticulitis diagnosis and treatment (N=114)

Variable	CVID (N=35) n (%)	No CVID (N=79) n (%)	OR (95%CI)	P-value
Complicated diverticulitis	7 (20.0)	17 (21.5)	0.91 (0.34-2.45)	0.854
Inpatient treatment	18 (51.4)	36 (45.6)	1.27 (0.57-2.81)	0.563
Surgical intervention	8 (22.9)	13 (16.5)	1.50 (0.56-4.04)	0.418
Recurrent diverticulitis	11 (31.4)	19 (24.1)	1.45 (0.60-3.49)	0.411

CVID, common variable immunodeficiency; OR, odds ratio; CI, confidence interval

Table 5 Associations between IVIG and diverticulitis among patients with CVID (N=35)

Variable	CVID IVIG (N=18) n (%)	CVID without IVIG (N=17) n (%)	OR (95%CI)	P-value
Complicated diverticulitis	2 (11.1)	5 (29.4)	0.30 (0.05–1.82)	0.228
Recurrent diverticulitis	4 (22.2)	7 (41.2)	0.41 (0.09–1.78)	0.289

IVIG, intravenous immunoglobulin; CVID, common variable immunodeficiency; OR, odds ratio; CI, confidence interval

and 2 patients had fistulizing complications. The mean length of stay for these patients was also similar (6.8 days, n=5 vs. 6.67 days, n=12; data was missing for 2 patients with CVID and 5 patients without CVID, who were excluded).

In the case cohort, 60% (17/28) of patients with uncomplicated diverticulitis were treated as outpatients with oral antibiotics. Only 1 returned to the emergency department and was found to have progression to complicated diverticulitis that eventually required surgical intervention. In the control cohort, 63% (43/62) patients with uncomplicated diverticulitis were treated as outpatients with oral antibiotics, and none of them required re-evaluation or admission to the hospital. Among all patients treated as outpatients, 24% (4/17) of the case cohort and 23% (10/43) of the control cohort developed recurrent diverticulitis.

Discussion

The risk factors for acute diverticulitis include genetic factors, consumption of a low-fiber diet, and lifestyle factors such as physical inactivity, obesity and smoking [11]. Our study found that patients with CVID who present to an emergency room with abdominal pain and undergo CT examination have lower odds of acute diverticulitis when compared to matched control patients without CVID who present to the emergency room with abdominal pain and undergo CT examination. Prior work by Hwang *et al* has shown a higher incidence of diverticulitis in patients who are organ transplant recipients and on long-term steroid treatment, and one could expect a higher incidence in CVID [10]. The reasons for lower odds of diverticulitis in CVID patients undergoing CT for abdominal pain remain to be elucidated; potential explanations include altered inflammatory responses and immune dysregulation in CVID affecting disease manifestation. The immune response in diverticulitis is primarily mediated by macrophages [12], and there is a pathophysiological basis for an association with CVID, as these patients demonstrate a constitutively activated phenotype of macrophages [13]. In addition, microbiome alterations have been hypothesized to play a role in the development of diverticulitis, which is also affected in patients with CVID. Our findings, however, do not show such an association, and additional studies on this topic are needed to further elucidate these findings.

To our knowledge this is the first study that has aimed to assess the risk of diverticulitis in patients with CVID who presented to the emergency department with abdominal pain and had CT imaging, compared to controls without CVID who present to the emergency room with abdominal pain and undergo CT examination.

Medication use, such as steroids and NSAIDs, as well as older age and certain comorbidities, have been associated with an increased risk of severe diverticulitis [11]. Given their immunosuppressed state, patients with CVID would be expected to have more severe diverticulitis, yet our study found no significant differences in the severity of diverticulitis between patients with CVID and controls. Furthermore, there was no statistically significant difference between CVID patients who received IVIG vs. those who did not in terms of severity and recurrence.

IVIG is recommended for reducing the frequency and severity of infections in patients with CVID [14]. Its efficacy for respiratory infections is well documented, but for gastrointestinal infections it has not been established. Busse *et al* reported a reduction in the incidence of pneumonias after IVIG treatment of patients with CVID [15]. It has been shown to independently decrease the severity of infections in certain contexts, such as sepsis [16], but is not recommended for routine use in the general population, given the low quality of evidence. Prospective studies on the use of IVIG in patients with CVID are needed to show whether IVIG reduces the risk and severity of diverticulitis in these patients.

According to a study using the nationwide inpatient sample (NIS), 10% of admissions for acute diverticulitis required surgical intervention and 4% required percutaneous drainage [17]. Our data set reported a trend towards a higher rate of surgical intervention in the CVID group (22.9% vs. 16.5%), but this was not statistically significant. The rates of surgical intervention in NIS databases may be lower compared to our study, because they only report on inpatient events, whereas our data include surgical interventions during admission or within a few months of the initial episode (for ongoing symptoms). The rates of percutaneous drainage were low and comparable in both groups (2.8% vs. 3.8%).

Furthermore, the data on patients treated as outpatients was also similar between both groups, with respect to return for hospitalization, complications and recurrence, which adds evidence that patients with CVID have similar outcomes overall, when compared to matched controls without CVID.

We found a numerically higher incidence of recurrent acute diverticulitis in the CVID group (31.4% vs. 24.1%) that did not reach statistical significance. The rates of recurrence are similar to those in previous studies reporting rates of 19-36% [18,19].

The strengths of our study are its multi-center design, with a large sample size and exact matching to limit confounding variables. In addition, to our knowledge this is the first study to evaluate the association between CVID and diverticulitis. One of the limitations of the study is its retrospective observational design. Since the data were obtained retrospectively through the electronic health record, it is possible that patients may also have presented to hospitals outside our health system for episodes of diverticulitis.

Overall, our study found that patients with CVID and abdominal pain evaluated in the emergency room had lower odds of diverticulitis than matched controls. The severity of diverticulitis was similar among CVID patients and controls. Prospective registries of patients with CVID can assess the longitudinal incidence of diverticulitis to help corroborate these findings.

Summary Box

What is already known:

- Common variable immunodeficiency (CVID) is associated with multiple gastrointestinal conditions, including inflammatory bowel disease, microscopic colitis, and CVID-enteropathy, due to immune dysregulation and gut microbiota alterations
- Immunocompromised patients are generally considered to be at higher risk for and more severe presentations of acute diverticulitis

What the new findings are:

- In a matched cohort of 1,392 patients, CVID was associated with significantly lower odds of computed tomography (CT)-confirmed acute diverticulitis among emergency room patients undergoing CT for abdominal pain (odds ratio 0.44, 95% confidence interval 0.30-0.66; P<0.001)
- This is the first study to evaluate the association between CVID and acute diverticulitis

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Supplementary material

Supplementary Table 1 Modified Hinchey classification for acute diverticulitis

Stage	Classification	Description
0	Mild clinical diverticulitis	Clinically mild diverticulitis managed in the outpatient setting
Ia	Confined pericolic inflammation or phlegmon	Inflammation or phlegmon confined to the pericolic region
Ib	Confined pericolic abscess (≤5 cm)	Pericolic or mesenteric abscess ≤5 cm
II	Pelvic, distant intra-abdominal, or retroperitoneal abscess	Pelvic, distant intra-abdominal, or retroperitoneal abscess >5 cm
III	Generalized purulent peritonitis	Perforated diverticulitis causing generalized purulent peritonitis (non-feculent)
IV	Generalized fecal peritonitis	Free perforation with fecal contamination causing generalized fecal peritonitis

Modified from Hinchey et al. with revisions by Kaiser et al. (2005). Stage 0 was added to reflect outpatient management of mild disease