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REVIEW

Gastrointestinal Manifestations of Common Variable Immunodeficiency: A Mentored Review

Abdillahi Ahmed[1] · **William King**[2] · **Anil Sharma**[2]

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Abstract

Background Common variable immunodeficiency (CVID) is an umbrella term for numerous primary immunodeficiency syndromes characterized by B-cell, and sometimes T-cell, impairment. While CVID is commonly associated with recurrent sinopulmonary infections, gastrointestinal (GI) disease—often presenting atypically due to immune dysregulation—can significantly the increase morbidity and mortality of those affected.

Objectives This review summarizes the diagnostic criteria, epidemiology, and GI manifestations of CVID to increase awareness among general practitioners and gastroenterologists. This review may help facilitate prompt diagnosis and treatment of affected patients.

Methods We conducted a narrative review of the literature focusing on the GI manifestations of CVID. This review investigates the GI infections, gastric and bowel diseases, liver involvement, and malignancies associated with this immunodeficiency.

Results There is no universal definition for CVID, but rather several commonly used diagnostic criteria. Patients with CVID are susceptible to GI infections including those caused by Giardia, norovirus, Salmonella, Campylobacter, and cytomegalovirus. Gastric diseases such as atrophic gastritis and pernicious anemia may present atypically. Bowel involvement may include nodular lymphoid hyperplasia, small intestinal bacterial overgrowth, CVID enteropathy, celiac-like disease, and inflammatory bowel-like colitis. Liver involvement can include autoimmune hepatitis, nodular regenerative hyperplasia, and viral hepatitis. In addition, patients with CVID may have a higher incidence of malignancies such as lymphoma and gastric cancer compared to the general population.

Conclusion CVID is associated with a broad spectrum of infectious and noninfectious GI manifestations that can increase the morbidity and mortality of affected patients. Increased awareness of these complications may facilitate earlier diagnosis and effective management.

Keywords Common variable immunodeficiency · Gastrointestinal manifestations · Gastroenteritis · Enteropathy · Malignancy

Introduction

Common variable immunodeficiency (CVID) comprises a heterogeneous spectrum of hypogammaglobulinemia syndromes caused by impaired B-cell differentiation, often accompanied by T-cell abnormalities [1]. It is the most common symptomatic primary immunodeficiency, with a prevalence between 1:50,000 to 1:25,000 and equal sex distribution [2, 3]. Most cases are sporadic, yet 20% display a familial inheritance pattern [3]. The pathogenesis of CVID remains poorly understood, but monogenic, polygenic, and epigenetic mechanisms have been identified [4–6]. Due to its variable presentation, there is an average diagnostic delay of 4 to 5 years, which is more prolonged in those with disease onset prior to the age of 10 [2].

Immune globulin administration, via intravenous (IVIG) or subcutaneous route, is the mainstay of CVID treatment and can reduce the incidence of infectious

✉ Abdillahi Ahmed
abdiahmed@ufl.edu

[1] Department of Internal Medicine, University of Florida College of Medicine, Gainesville, FL 32610, USA

[2] Division of Gastroenterology, Hepatology & Nutrition, University of Florida College of Medicine, Gainesville, FL 32608, USA

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Table 1 Comparison of commonly used CVID diagnostic criteria

Criteria characteristics	Ameratunga et al. (2013) [10]	ESID (2014) [11]	Bonilla et al. (2016) [12]
Diagnosis of exclusion	+	+	+
Low IgG required	+	+	+
Low IgA and/or IgM required		+	+
Age must be > 4	+	+	
Symptoms required		+	
Impaired vaccine response required			+
A "definite" diagnosis is defined			+
A "probable" diagnosis is defined	+	+	
A "possible" diagnosis is defined	+		

ESID European Society for Immunodeficiencies, *IgG* immunoglobin G, *IgA* immunoglobin A

complications. Hematopoietic stem cell transplantation has been reported to improve immune dysregulation and cure hypogammaglobulinemia in patients with CVID, but at the cost of high treatment-related mortality [7]. Recurrent sinopulmonary infections are the most common sign of CVID, but chronic lung disease, autoimmunity, gastrointestinal (GI) disease, and malignancy can occur [8]. Diagnosis can be difficult due to diverse clinical presentations and the absence of universal diagnostic criteria. The European Society for Immunodeficiencies and Pan-American Group for Immunodeficiency (ESID/PAGID) published the first criteria in 1999 [9]. Since then, commonly cited diagnostic criteria include those from Ameratunga et al. [10], the European Society for Immunodeficiencies (ESID) [11], and Bonilla et al. [12], all of which overlap (Table 1) [10–12]. Notably, CVID remains a diagnosis of exclusion in all definitions. As advancements in molecular genetics lead to the discovery of causative mutations, patients may be reclassified as having a mutation-based immunodeficiency that is not CVID but rather phenotypically *CVID-like* [12, 13]. Nonetheless, genetic testing is essential to identify patients initially diagnosed with CVID who may benefit from directed therapies.

GI disease is reported in more than 20% of studied CVID populations [14, 15]. This complication contributes to significantly increased mortality compared to age and sex-matched controls [8]. In patients with CVID, IVIG binds gut microbiota less effectively, diminishing its effectiveness for GI infections [16]. Immunoglobulin A (IgA) deficiency is common in CVID and increases susceptibility to GI infections [17]. GI infections may respond atypically to standard treatments and exhibit protracted clinical courses in patients with CVID. Non-infectious conditions can mimic established GI disorders but present with distinct histopathological findings, requiring specific therapies. This review aims to familiarize general practitioners and gastroenterologists in the recognition and management of the GI manifestations of CVID.

Methods

An electronic search of PubMed and Google Scholar included the search terms "common variable immunodeficiency," with "gastroenteritis," "gastritis," "enteropathy," "autoimmunity," "hepatitis," or "malignancy." Additional articles were found by reviewing the references used in index articles. Also, by reviewing articles which cited index articles. Randomized controlled trials, meta-analyses, systematic reviews, practice guidelines, observational studies, and case reports were included. Thematic analysis of the reviewed literature was utilized to identify recurrent themes, determine inclusion in this narrative, and format a manuscript structure tailored to our aims.

Infection

Giardia sp., Norovirus*, Salmonella spp.,* and *Campylobacter spp.* are leading causes of infectious gastroenteritis in patients with CVID [18, 19]. Symptoms are generally nonspecific and range from self-limiting to chronic to refractory abdominal pain, diarrhea, and weight loss. A positive association has been shown between *Giardia*, *Salmonella*, and *Campylobacter* infections in CVID patients with undetectable serum IgA levels, which is unsurprising given the established role of IgA in mucosal defense [17, 20]. Norovirus and cytomegalovirus infections rarely have clinical significance in immunocompetent individuals; however, their complications can be severe with CVID.

Giardia

Giardiasis is the most common GI infection in CVID, affecting 13–14% of patients [17, 18]. In a systematic review by Díaz-Alberola et al. in 2022, 30% and 35% of patients with CVID and giardiasis experienced chronic or refractory infection, respectively. Protein loss associated with giardiasis can also complicate maintenance of target immunoglobin G (IgG) levels with standard IVIG dosing [20]. Microscopy with direct fluorescent antibody testing, preferably via three stool samples collected over several days, is the diagnostic gold standard. High sensitivity stool polymerase chain reaction (PCR) is increasingly available, however detection of non-viable pathogen DNA can lead to high-false positive rates [21]. First line therapy for giardiasis is metronidazole, however tinidazole and nitazoxanide are also effective [22].

Norovirus

Norovirus gastroenteritis is a leading cause of gastroenteritis worldwide. Pikkarainen et al. found its prevalence to be 7% in a population of 132 CVID patients [19]. Although norovirus affects 19% of the general global population, it has been found in up to 100% of those with CVID enteropathy [23, 24]. Chronic norovirus infections have been identified as an etiology of enteropathy in patients with CVID [25]. Therefore, patients with CVID and concurrent norovirus infections should be monitored closely for symptom resolution, and alternative treatment should be considered when infections are prolonged. Stool PCR is the mainstay of diagnosis. There is no standard treatment for norovirus. However, ribavirin, oral immunoglobulins, and nitazoxanide have had variable success in immunocompromised patients [26–28].

Salmonella

Salmonellosis can affect 6% of patients with CVID [18]. Indications for antibiotic treatment include those at high risk for invasive disease, such as the immunocompromised. Hypogammaglobulinemia alone has been reported not to increase the risk of salmonella infections [29]. However, defective cell mediated immunity, which can be present in CVID, has been shown to increase the risk for, and severity of, salmonellosis [1, 30]. Furthermore, achlorhydria is a common occurrence in CVID that may increase susceptibility to severe salmonella infections [31, 32]. Stool culture is the recommended initial diagnostic test, detecting only viable organisms, thus active infection, and provides antimicrobial susceptibility. Ceftriaxone and ciprofloxacin are common initial treatments, while use of ampicillin, azithromycin, or trimethoprim-sulfamethoxazole can be used as alternatives guided by susceptibilities [33].

Campylobacter

Patients with CVID and campylobacteriosis typically have more severe immunodeficiency than those who do not acquire this infection [34]. Campylobacteriosis can affect 4% of patients with CVID, and the rate of recurrent infection is as high as 42% to 71% [18, 34, 35]. These recurrent infections are often with different strains of *Campylobacter spp.*, which suggests either frequent reinfections or colonization with atypical strains [34]. Stool culture is the preferred diagnostic test, and azithromycin is the first line treatment due to growing fluoroquinolone resistance. Neomycin, tigecycline, ertapenem, and chloramphenicol can be effective in patients who fail other treatments [35].

Cytomegalovirus

The prevalence of seropositive cytomegalovirus (CMV) ranges from 40 to 100% in the general population [36]. Yet, symptomatic GI CMV infection is rarely reported in patients with CVID [14]. This may be because CVID patients with severe T-cell defects and/or opportunistic infections such as CMV have been reclassified as having a *combined immunodeficiency* since 2009 [37]. GI CMV infection must not be overlooked in CVID due to its high morbidity, which can necessitate parental nutrition or total colectomy [38–40]. It is important to be familiar with the associated window period of CMV as infected individuals can be seronegative despite having infection, thus making seropositivity alone an insufficient diagnostic test. The administration of IVIG, which is a pooled blood product, can cause seropositivity, further complicating the use of serologic testing [41]. Therefore, colonic biopsies with immunohistochemical staining for CMV are appropriate when there is clinical concern for CMV colitis. Treatment typically involves intravenous ganciclovir, followed by oral valganciclovir once the patient is clinically improving. Foscarnet remains an alternative therapy for patients intolerant of ganciclovir.

Gastric Disease

Atrophic Gastritis

The etiology of atrophic gastritis (AG) is generally either infectious, resulting from *Helicobacter pylori* (*H. pylori*) infection, or autoimmune, mediated by parietal cell autoantibodies. In 2019, Pikkarainen et al. found that the prevalence of biopsy-proven AG was 17% in CVID patients with nonspecific GI symptoms, while in 2016 Jørgensen

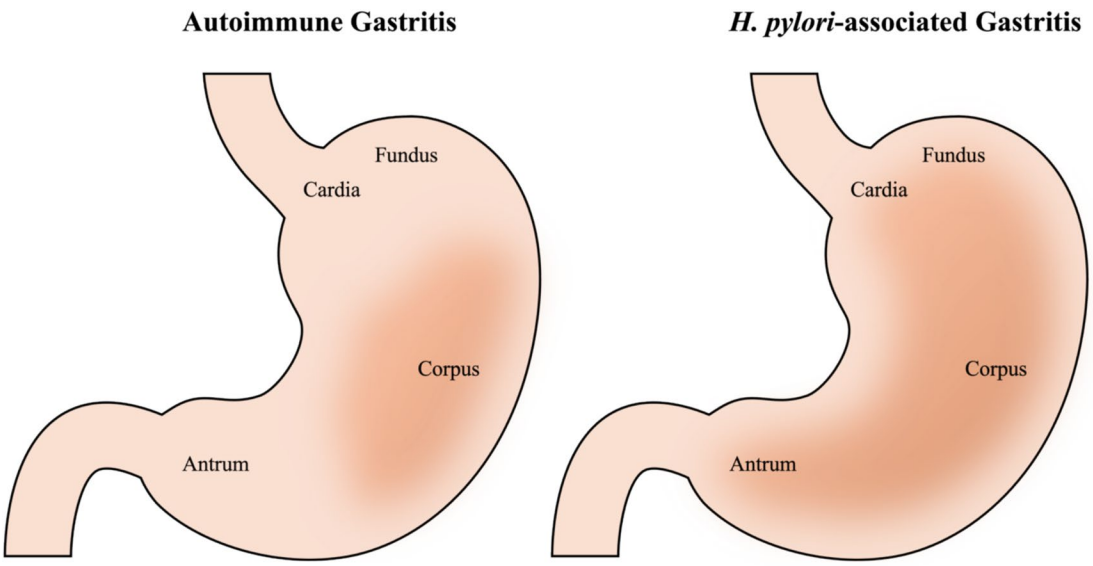

Fig. 1 Comparing the typical anatomical location of metaplastic atrophic gastritis (shaded regions) seen with autoimmune gastritis and *H. pylori* infection. Autoimmune gastritis is associated with corpus-restricted gastritis, whereas *H. Pylori* is associated with multifocal atrophic gastritis. Atrophic gastritis in CVID can grossly resemble autoimmune gastritis without the presence of autoantibodies [19]

et al. reported a prevalence of 18% in a cohort including asymptomatic CVID patients [19, 42]. Atrophic gastritis associated with CVID is unique given it can be corpus-restricted, which is suggestive of autoimmune gastritis, but in the absence of parietal cell autoantibodies (Fig. 1) [19]. There is an increased risk of *H. pylori* developing secondary antibiotic resistance, therefore becoming chronic, in CVID patients due to recurrent antibiotic use for infections. Gastric cancer can occur in up to 1.8% of patients per year with AG. This incidence rises to 10% when intestinal metaplasia is present, and up to 73% when dysplasia is present [43]. It is important to maintain a high index of suspicion for AG in patients with CVID and obtain gastric biopsies if it is clinically suspected. Management includes treating underlying risk factors such as *H. pylori*, if present, and correcting associated vitamin and mineral deficiencies.

Pernicious Anemia

Pernicious anemia (PA) has a prevalence ~9% in CVID patients [44]. Those affected can be asymptomatic, have nonspecific symptoms such as fatigue and dyspnea, or in

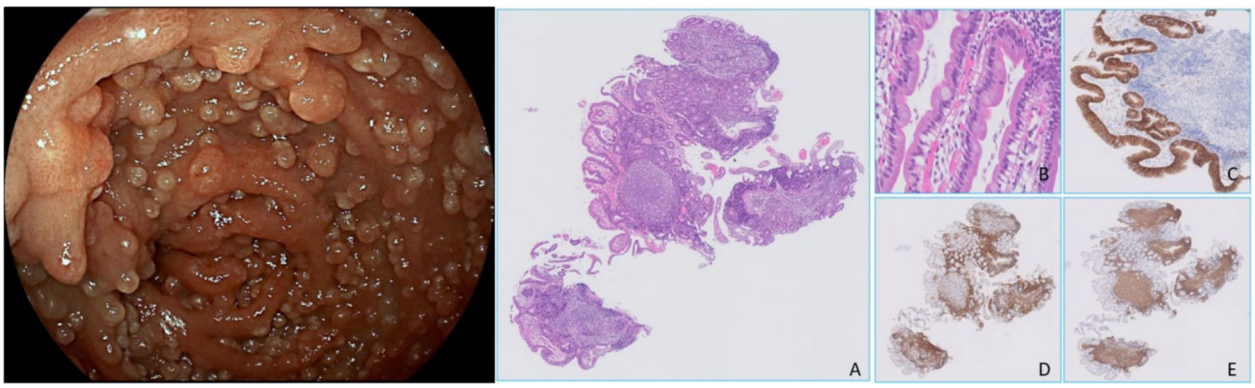

Fig. 2 Upper gastrointestinal endoscopy showing multiple nodules the in duodenal bulb. Histology of duodenal biopsy with follicular hyperplasia (**A**) and the presence of *Giardia lamblia* between the villi (**B**) (H&E stain). Immunohistochemical staining for CD138 (**C**) showing the near absence of plasma cells due to common variable immunodeficiency. Immunohistochemical CD3 (**D**) and CD20 (**E**) stains show the presence of T-lymphocytes and B-lymphocytes, respectively. Adapted by permission from BMJ Publishing Group Limited. [Innumerable nodules in all parts of the small intestine, Veghel et al. [54]

severe cases, experience subacute combined degeneration. There are variable diagnostic criteria for pernicious anemia. Low vitamin B12 plus the presence of intrinsic factor (IF) or parietal cell autoantibodies is highly suggestive of the diagnosis [45]. A PA-like syndrome can occur in CVID, characterized by achlorhydria, atrophic gastritis including the gastric antrum, and the absence of IF and parietal cell autoantibodies [46–48]. PA-like syndrome has been suggested to originate from dysregulated cellular immunity affecting gastric mucosa [48]. Treatment of PA often involves intramuscular cobalamin supplementation to bypass impaired IF-mediated enteral absorption. However, passive diffusion of cobalamin also occurs and oral supplementation has been shown to be effective [49–51].

Bowel Disease

Nodular Lymphoid Hyperplasia

Nodular lymphoid hyperplasia (NLH) is a benign condition characterized by small diffuse nodules of reactive lymphoid follicles along the GI tract, most commonly in the small intestine [52]. The reported prevalence of NLH is highly variable, ranging from 4–53% among different CVID patient populations [14, 42, 52]. CVID-associated NLH is often asymptomatic, with one study showing no association with GI symptoms [42]. The true prevalence of NLH may be underreported if asymptomatic patients do not undergo endoscopy. A nodular mucosa on seen on endoscopy or barium studies may be suggestive of NLH, but formal diagnosis requires histopathologic confirmation given its resemblance to polyposis syndromes (Fig. 2) [53]. Management involves treatment of associated conditions, which include immunodeficiency, giardiasis, and *H. pylori* infection [20, 53].

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) is defined as symptomatic GI distress caused by the presence of excessive colonic bacteria in the small bowel. Bloating is the most prominent symptom, however, abdominal pain, flatulence, and diarrhea are also common [55]. More than 40% of patients with CVID are reported to have SIBO, which can contribute to weight loss, anemia, and malabsorption [56]. Notably, its true prevalence may be underestimated due to frequent use of antibiotics for recurrent infections associated with CVID, which may diminish the utility of breath testing and minimize patient symptoms. The lack of IgA associated with CVID has been proposed as a risk factor for SIBO, although in 2021 Baniadam et al. found no significant difference in IgA between CVID patients with and without SIBO [56, 57]. When available, rifaximin is an effective treatment for SIBO [58].

Common Variable Immunodeficiency Enteropathy

CVID enteropathy does not have a universal definition, but several have been proposed (Table 2). We describe it as non-infectious and clinically significant chronic malabsorption in a patient with CVID with clinicopathologic distinctions from currently defined enteropathies. CVID enteropathy can resemble celiac disease and inflammatory bowel disease. This enteropathy is important to identify as it has been

Table 2 Proposed CVID enteropathy definitions in literature

Author	CVID enteropathy definition
Chapel H, Lucas M, Lee M, et al. (2008)	Biopsy-proven lymphocytic infiltration in lamina propria and interepithelial mucous with villous atrophy, insensitive to gluten withdrawal [44]
Malamut G, Verkarre V, Suarez F, et al. (2010)	Heterogeneous lesions including intraepithelial hyperlymphocytosis, villous atrophy, follicular lymphoid hyperplasia, and acute and/or chronic lesions of duodenitis [59]
Chapel H, Lucas M, Patel S, et al. (2012)	Enteropathy (unexplained—excluding infective, autoimmune, and gluten-sensitive enteropathies) [60]
Jørgensen SF, Trøseid M, Kummen M, et al. (2016)	Chronic diarrhea without infection [61]
Shulzhenko N, Dong X, Vyshenska D, et al. (2018)	Chronic diarrhea or unexplained weight loss greater than 5% of total body weight over the previous 6 months with changes in more than one parameter consisting of body mass index, serum albumin, serum protein and number of liquid stools [62]
van Schewick CM, Nöltner C, Abel S, et al. (2020)	Patients with longstanding diarrhea or proven mucosal abnormality on biopsy not attributable to infection [63]
Andersen IM, Jørgensen SF (2022)	Diarrhea for at least 3 months and an exclusion of infectious bacterial and parasite infection, but not norovirus (as this may be persistent and indicate a more severe disease) [64]
van Schewick CM, Lowe DM, Burns SO, et al. (2022)	Generic term for longstanding, non-infectious diarrhea with proven mucosal abnormalities [65]

shown to have a four-fold increased mortality risk compared to CVID patients without this condition [44].

Celiac-Like Disease

The prevalence of celiac disease (CD) is 1.4% in the general population compared to 9.2% in patients with CVID [66, 67]. The diagnosis is made on small bowel biopsy showing intraepithelial lymphocytosis, villous atrophy, and crypt hyperplasia. Up to 30% of CVID patients can show celiac-like small bowel lesions [67]. Reduced or absent plasma cells in the lamina propria should raise suspicion for CVID [68]. In 2012, Biagi et al. proposed that a histological response to a gluten-free diet (GFD) is the only means to distinguish CD from celiac-like disease [69]. Also, that the absence of HLA DQ2 and DQ8 alleles can reliably exclude CD. However, CVID patients with negative HLA typing can show histological improvement with a gluten free diet, raising uncertainty about the mechanism of celiac-like disease in CVID [59]. Serologic testing for CD is of no utility in CVID patients given their impaired immune response [70]. Distinction of these entities is important, as celiac-like disease may involve the use of steroids, biologics, and immunomodulators to achieve disease control [46, 68].

Inflammatory Bowel-Like Disease

The prevalence of inflammatory bowel disease (IBD) is reported between 4.2 and 5% in patients with CVID [8, 19]. Patients with CVID can have endoscopic lesions including colitis, ulcerations, crypt abscesses and destruction, and granulomas [57]. A common distinction between IBD-like disease in CVID and classic IBD is a paucity or absence of plasma cells and lack of IgA and IgM-producing cells in the lamina propria on histology [70, 71]. In 2006, Mannon et al. found IBD-like disease does not involve excess IL-23, IL-17, or TNF-α production by lamina propria mononuclear cells like in classical Crohn's disease, which provides more evidence that these two entities are distinct [72]. Treatment for IBD-like CVID and classic IBD are often similar involving immunomodulators and biologics.

Liver Disease

Autoimmune Disease

To date, four cases of autoimmune hepatitis (AIH) associated with CVID are reported in the literature [73–76]. AIH is a diagnosis of exclusion requiring a liver biopsy with compatible histological findings, such as lymphoplasmacytic interface hepatitis [77]. The presence of elevated liver enzymes, IgG, and characteristic antibodies support the diagnosis. AIH can be a diagnostic challenge in CVID when decreased antibody production is assured. Standard AIH treatment includes corticosteroids and immunomodulators. Liver transplantation may be considered for patients with refractory disease. Disease control has been reported with ursodeoxycholic acid and intravenous glycyrrhizin in the absence of immunosuppression agents [73]. Primary sclerosing cholangitis (PSC) is another immune mediated liver disease which lacks effective medical treatments, for which we found two cases associated with CVID published by Mahdavinia et al. in 2015 [78, 79]. PSC is associated with a significantly increased risk for colorectal cancer and cholangiocarcinoma, which may be amplified in patients with CVID who already have an increased GI cancer risk [79, 80]. Magnetic resonance imaging with cholangiopancreatography should be considered in patients with signs of cholestasis to facilitate early diagnosis.

Nodular Regenerative Hyperplasia (NRH)

Nodular regenerative hyperplasia is characterized by diffuse nodules of regenerative hyperplastic hepatocytes without surrounding fibrosis, which distinguishes this entity from cirrhosis and is proposed to be a response to hypoperfusion of hepatic parenchyma [81, 82]. The prevalence of NRH in CVID has been reported between 1 and 12% [8, 81, 83]. The true prevalence of NRH is likely higher as it can exist in the absence of laboratory or clinical evidence of liver dysfunction and requires biopsy with reticulin staining for diagnosis [81, 82]. NRH is of clinical significance since it can result in non-cirrhotic portal hypertension and its sequelae [82]. Further research is needed into appropriate management, as there is no data on the safety of transjugular intrahepatic portosystemic shunt placement for refractory ascites or variceal bleeding in CVID-related NRH. There is a theoretical risk that bypassing the liver, a site of complex immune activity, may further predispose these immunocompromised patients to infection [84].

Hepatitis C

Hepatitis C virus (HCV) infection demonstrates a more rapidly progressive and deleterious course in patients with primary immunodeficiencies, including CVID, compared to the those who are immunocompetent [85–87]. Patients with CVID had an increased risk of contracting hepatitis C from contaminated IVIG outbreaks in the United States and Europe between 1993–1994 [88]. However, subsequent advances in viral inactivation methods and donor screening have essentially eliminated this risk [89]. When there is clinical suspicion for HCV, diagnostic testing should

include viral load measurements, as the absence of anti-HCV antibodies cannot reliably exclude disease in the setting of hypogammaglobulinemia [90]. CVID-associated HCV has been shown to have a poor response to interferon, however, the efficacy of modern antivirals in this population is uncertain [90].

Malignancy

A systematic review and meta-analysis by Kiaee et al. in 2019 found the prevalence of malignancy to be 8.6% in a population of 8,123 CVID patients [80]. The most common malignancies reported were lymphoma and gastric cancer.

Lymphoma

Lymphoma is the most common malignancy in CVID, which affects 4.1% of these patients [80]. Furthermore, Non-Hodgkin's lymphoma (NHL) is the most common subtype. CVID-associated NHL occurs predominantly in females, is usually of extranodal origin, and of B-cell type [14, 91]. Gastroenterologists should be aware of this association, since the GI tract is the predominant site in 30–40% of extranodal lymphomas [92]. Lymphoma is also the second leading cause of death in CVID, after chronic lung disease [8]. There may be shared genetic substrates between NHL and CVID, but these are beyond the scope of this review paper [93]. Chronic GI infections, which are highly prevalent among patients with CVID, are also independent risk factors for NHL [80, 93].

Gastric Cancer

Gastric cancer incidence in CVID is reported to be 10 to 47 times that of the general population [31, 94]. There is no comprehensive mechanism to explain these findings, but there are independent modifiable risk factors for gastric cancer associated with CVID, including chronic *H. pylori* and gastric atrophy [95]. *H. pylori* may be difficult to eradicate in CVID patients due to resistance from recurrent antibiotic exposure. One study involving screening endoscopy in CVID patients found significantly higher rates of precancerous gastric lesions compared to a control group, which highlights a potential role for gastric cancer screening in this population [96]. In 2011, Dhalla et al. proposed a selective approach to endoscopic gastric cancer screening in CVID patients with *H. pylori*, pernicious anemia, or dyspepsia symptoms, but there is still an increased risk for gastric cancer in CVID patients without these conditions [97].

Conclusion

CVID is most often characterized by recurrent sinopulmonary infections. However, there are numerous infectious and noninfectious GI manifestations that can occur with this disorder. We have reviewed the diagnostic criteria and GI disease associated with CVID to help general practitioners and gastroenterologists identify and manage affected patients. Further research is needed into the management of CVID-associated GI disease, as IVIG has minimal efficacy. This review is especially important given significant overlap between established GI disorders and CVID-associated GI disease, the latter of which often require a unique and nuanced treatment strategy.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors do not have any financial or non-financial interests to disclose.

Ethical approval Ethical approval was not required for this mentored review.

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