Hepatic complications in common variable immunodeficiency (CVID)

Complicações hepáticas na imunodeficiência comum variável (IDCV)

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ABSTRACT

Primary immunodeficiencies (PIDs), also known as inborn errors of immunity (IEIs), comprise a heterogeneous group of disorders characterized by increased susceptibility to infections, autoimmunity, autoinflammatory disorders and malignancies. Common variable immunodeficiency (CVID) is the most prevalent symptomatic PID and is characterized by markedly reduced serum immunoglobulin levels and impaired vaccine-specific antibody responses. Hepatic involvement affects approximately 10% of patients and requires a high index of clinical suspicion. The spectrum of liver disease in CVID is broad, encompassing nodular regenerative hyperplasia (NRH), idiopathic non-cirrhotic portal hypertension (INCPH), viral hepatitis, autoimmune hepatitis and hepatic neoplasia. Early recognition and accurate diagnosis of hepatic manifestations are crucial for preventing disease progression and enabling timely management of complications. Therapeutic options remain limited and are directed toward the prevention and treatment of subsequent complications. Optimal patient care relies on a multidisciplinary approach integrating expertise from Allergy/immunology, Internal Medicine, and Hepatology.

Key words: *Common variable immunodeficiency, hepatic diseases, primary immunodeficiencies.*

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RESUMO

As imunodeficiências primárias (IDP), recentemente designadas por erros inatos da imunidade (EII), constituem um grupo heterogéneo de patologias caracterizadas por uma maior suscetibilidade a infeções, autoimunidade, doenças autoinflamatórias e neoplasias. A imunodeficiência comum variável (IDCV) é a IDP sintomática mais prevalente, caracterizando-se por níveis séricos de imunoglobulinas significativamente reduzidos e respostas humorais deficitárias à vacinação. O envolvimento hepático ocorre em aproximadamente 10% dos doentes, exigindo um elevado índice de suspeição clínica. O amplo espetro de manifestações hepáticas na IDCV inclui hiperplasia nodular regenerativa (HNR), hipertensão portal não cirrótica idiopática (HPNCI), hepatites virais, hepatite autoimune e neoplasia hepática. O reconhecimento e diagnóstico precoces das manifestações hepáticas são essenciais para prevenir a progressão da patologia e permitir a abordagem atempada das complicações. As opções terapêuticas permanecem limitadas, focando-se na prevenção e tratamento das mesmas. A otimização da gestão nestes doentes requer uma abordagem multidisciplinar, incluindo especialistas em Imunoalergologia, Medicina Interna e Hepatologia.

Palavras-chave: Doenças hepáticas, imunodeficiência comum variável, imunodeficiências primárias.

Impact statement: Emerging evidence highlights the importance of early recognition and multidisciplinary management of hepatic complications in CVID, emphasizing their prognostic impact and the need for individualized therapeutic strategies.

INTRODUCTION

Common Variable Immunodeficiency

Primary immunodeficiencies (PIDs), currently referred to as inborn errors of immunity (IEIs), encompass a diverse group of disorders caused by genetic mutations that impair both innate and adaptive immunity. According to the 2024 Classification by the International Union of Immunological Societies (IUIS), 555 distinct IEIs have been identified (1). Predominantly antibody deficiencies, including common variable immunodeficiency (CVID), are the most common PIDs in adults, accounting for approximately 50% of all cases (2).

CVID, first described in 1954, is the most frequently diagnosed symptomatic PID in adults, with prevalence estimates ranging between 1:25,000 and 1:50,000. Clinical onset typically occurs between the age of 20 and 45 years (3,4).

The disorder is characterized by impaired B-cell differentiation, leading to a reduction in plasma cells, class-switched memory B cells, antibody production and, consequently, a compromised humoral immune response (5,6,7). T-cell abnormalities, such as decreased naive CD4+ T cells, have also been observed and may contribute to organ-specific lymphoproliferative disorders, including liver disease (7). The European Society for Immunodeficiencies (ESID) diagnostic criteria are summarized in Table I (8).

CVID is characterized by variable hypogammaglobulinemia with reduced levels of IgG, IgA and/or IgM. Symptom onset can occur at any age, though diagnosis is often delayed due to clinical heterogeneity. The majority of patients develop symptoms in the second or third deca-

Table 1. Diagnostic criteria for common variable immunodeficiency (CVID) according to the European Society for Immunodeficiencies (ESID). Adapted from (8).

Probable CVID	All of the following conditions: • Significant decrease in IgG (below two standard deviations from the age-adjusted mean); • Significant decrease in IgA and/or IgM; • Development of immunodeficiency after the age of 2 years; • Absence of isohemagglutinins and/or poor response to vaccination; • Exclusion of other causes of hypogammaglobulinemia.
Possible CVID	All of the following conditions: • Significant decrease in IgG, IgM, or IgA (below 2 standard deviations from the age-adjusted mean); • Development of immunodeficiency after the age of 2 years; • Absence of isohemagglutinins and/or poor response to vaccination; • Exclusion of other causes of hypogammaglobulinemia.

des of life, with no significant differences between males and females. Genetic abnormalities are identified in approximately 10–20% of cases (7,9,10).

Clinically, CVID presents with recurrent infections, neoplasms, autoimmune diseases, granulomatous conditions, hepatopulmonary disorders and polyclonal lymphoproliferation (7,11,12). Ribeiro Rodero *et al.* conducted a descriptive case series study involving 36 CVID patients and found that non-infectious manifestations were reported in 89% of cases (13).

In this context, secondary immunodeficiencies must be excluded, including those due to hematologic, autoimmune or renal disorders, HIV infection, malnutrition, chemotherapy or immunosuppressive therapies (14).

Non-infectious comorbidities, especially chronic lung disease, autoimmune cytopenias, malignancy and CVID-associated liver disease, significantly impact management and prognosis in CVID (3,5,14).

METHODS

In this narrative review, a literature search was conducted in the PubMed/MEDLINE database using the following keywords: "Common Variable Immunodeficiency", "Hepatic Diseases" and "Primary Immunodeficiencies." Articles published between 2012 and 2025 were included, yielding 34 relevant publications. No language restrictions were applied.

RESULTS AND DISCUSSION

Common Variable Immunodeficiency and Hepatic Complications

Hepatic involvement in CVID shows variable prevalence, with recent meta-analyses reporting rates ranging from 9% to 79% (4), while other studies estimate that approximately 10% of patients are affected (11).

Manifestations include hepatomegaly, hepatic granulomas, nodular regenerative hyperplasia (NRH), chronic and autoimmune hepatitis, liver cirrhosis, primary biliary cholangitis (PBC), and primary sclerosing cholangitis. These conditions may progress to liver dysfunction and complications, such as portal hypertension (PH), esophageal varices (with risk of variceal bleeding), spontaneous bacterial peritonitis, hepatopulmonary syndrome, and hepatic encephalopathy (15).

Clinical presentation ranges from asymptomatic cases to a wide array of signs and symptoms, including nausea, vomiting, fatigue, ascites, jaundice, pruritus, peripheral edema, hepatomegaly, splenomegaly, elevated liver enzymes, and variceal bleeding (7,11,12,15,16).

Predictors of mortality in CVID patients with hepatic involvement include fibrosis, increased hepatic resistance and PH, which may lead to hypersplenism and hematological abnormalities, such as anemia, leukopenia, and thrombocytopenia (17). In a large cohort study in the United States, CVID patients with hepatic complications had significantly reduced survival, with a hazard ratio (HR) of 2.48 compared to those without (18).

Halliday *et al*. reported that among 218 patients, hepatic involvement was associated with higher rates of non-infectious CVID complications, namely interstitial lung disease and intestinal pathology. NRH was observed in 63.8% of patients and 95.3% showed fibrosis on biopsy. Increased hepatic resistance was associated with PH and higher mortality compared to those without liver involvement (19).

These findings underscore the importance of close monitoring and early detection of these conditions.

Etiopathogenesis of Liver Disease in CVID

The etiology of hepatic involvement in CVID is complex and not yet fully understood, but evidence points to primary B-cell dysfunction, T-cell abnormalities and impaired antigen-presenting cell function as key contributors (7).

Defective B-cell differentiation into plasma cells and memory B cells and dysregulated signaling via CD70 and CD86, along with abnormalities in B-cell receptors, toll-like receptors (TLRs) and interferon-α, compromises humoral immunity and increases susceptibility to recurrent infections (15).

T-cell defects, including reduced numbers of CD4+ and regulatory T cells, expansion of CD8+ T cells, impaired proliferation, cytokine dysregulation and heightened apoptosis, further contribute to immune dysregulation (15).

Moreover, decreased myeloid and plasmacytoid dendritic cells are associated with autoimmunity, granulomas and splenomegaly. Regarding the genetic contribution to CVID, approximately 5–25% of patients have a positive family history, with most cases exhibiting an autosomal dominant inheritance pattern. To date, a growing number of monogenic defects arise in CVID-like patients. However, current evidence suggests that CVID is predominantly polygenic rather than monogenic (10). Emerging evidence suggests that specific genetic variants, such as NFKB1, NFKB2, CTLA4 and LRBA, affect immune regulatory pathways and contribute to phenotypic heterogeneity in CVID. These variants have been associated with an increased risk of non-infectious manifestations, including hepatic involvement such as NRH and PH (10,18). The etiology of hepatic involvement in CVID appears to be linked to immune dysregulation, promoting NRH, lymphocytic infiltration and granulomatous disease, as well as infectious factors (such as viral hepatitis and extra-intestinal localization of *Giardia lamblia*) and neoplasms (including liver tumors, extra-nodal lymphoid neoplasms, and metastatic involvement from gastrointestinal malignancies). Recent data indicate that CVID patients with duodenal lymphocytic infiltration are highly susceptible to hepatic involvement, predominantly NRH. Liver injury is closely linked to lymphocytic enteropathy, pointing to a potential pathogenic role of the gut-liver axis. The simultaneous presence of lymphocyte-rich infiltrates and hepatocyte degeneration on liver electron microscopy further supports a shared immune-mediated mechanism, suggesting that intestinal and hepatic pathology in this CVID subset reflects a common underlying immunological process rather than isolated organ involvement. (15, 20)

Clinical and Laboratory Spectrum of Liver Disease in CVID

NRH is the most common form of hepatic involvement in patients with CVID. Studies have shown significant variability in the prevalence of NRH, with two studies reporting prevalences of 5% and 12% (18). The diagnosis of NRH and granulomatous hepatitis is rarely made outside the context of primary immunodeficiency, so CVID should always be considered in these patients (21).

Hepatic involvement is often associated with elevated levels of alkaline phosphatase (ALP) and aspartate aminotransferase (AST), with the most common conditions being primary biliary cholangitis, granulomatous liver disease and idiopathic non-cirrhotic portal hypertension (INCPH), including NRH (22).

NRH is defined by the focal or diffuse development of hepatocellular nodules, typically less than 3 mm in diameter, which can be detected by hematoxylin-eosin and reticulin staining. These nodules lead to compression of peripheral sinusoids, where perisinusoidal fibrosis may

occur (3). NRH can be associated with autoimmune diseases, immunodeficiencies and conditions disrupting hepatic blood circulation.

Most patients are asymptomatic, with progressive ALP elevation being the most established predictor of NRH in CVID. Approximately 50% of patients exhibit mildly elevated transaminases. Late complications include esophageal varices, jaundice, ascites, hepatosplenomegaly, neutropenia, and thrombocytopenia (6,12,15,18).

NRH is caused by intrahepatic vasculopathy, leading to hepatocyte injury and nodule formation, which compress hepatic sinusoids as well as portal and central veins. These phenomena induce INCPH, perisinusoidal fibrosis and potentially liver cirrhosis. NRH is the primary cause of INCPH in Western countries (18) and represents the most common histological finding in CVID patients with hepatic involvement, affecting 41–87% of patients undergoing liver biopsy. Its occurrence does not correlate with the age of onset, age at diagnosis or duration of immunoglobulin replacement therapy (18).

INCPH is a well-known complication in CVID, representing a cause of intrahepatic pre-sinusoidal PH. Its pathogenesis is unclear, with proposed mechanisms including increased splanchnic blood flow, chronic microangiopathy of the portal venules, immune dysregulation and increased susceptibility to infections (4,11).

INCPH presents several predisposing factors, including HIV infection, immune disorders, hypercoagulability, genetic predisposition and chronic or recurrent infections (21). It primarily manifests as PH, with bleeding from esophageal varices being the most common complication, observed in 85–95% of patients at diagnosis. Since liver function is usually preserved, the prognosis of variceal bleeding tends to be more favorable than in cirrhotic patients (11).

INCPH requires a high index of suspicion, especially in those with ascites, which occurs in 50% of patients. It may develop in the context of infections or esophageal variceal rupture. Portal vein thrombosis is common, especially in HIV-infected patients or those with prior bleeding episodes. Signs of hypersplenism, including anemia, thrombocytopenia, leukopenia and splenomegaly, may also be present, while hepatic encephalopathy is a rare finding (11,17). Enteropathy frequently associated with CVID may contribute to vasculopathy of the terminal branches of the portal vein, promoting INCPH (23).

Globig *et al.* reported that clinically significant PH develops later than other clinical CVID manifestations. Among 479 CVID patients, 27 developed PH and 21 underwent liver biopsy, with only two cases of cirrhosis. Patients with PH had elevated alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT), while total bilirubin levels were not significantly elevated. Hepatic dysfunction was observed in the form of decreased albumin levels. They had higher mortality rates and more complications related to CVID compared to those without PH (24).

Hepatopulmonary syndrome (HPS) is a rare but severe complication of liver disease, characterized by pulmonary vascular dilatations causing hypoxemia. This condition occurs in patients with chronic liver disease, especially cirrhosis, and results in the clinical triad of liver failure, pulmonary vessel dilation and hypoxemia (25,26).

Viral hepatitis has been reported in CVID, with a significant number of iatrogenic hepatitis C (HCV) cases reported in the 1990s due to infusion of intravenous immunoglobulin contaminated with the HCV. Recent cohort studies have shown a reduced prevalence of viral hepatitis due to increased efficacy in preventing contamination from blood products (16). Patients with CVID are at increased risk of chronic hepatitis due to impaired viral clearance (27). Accurate diagnosis requires serological and viral load testing, as antibodies such as anti-HCV may be falsely negative due to immunodeficiency (31).

Hepatic neoplasms are rare but have been described in CVID. In an Italian cohort of 455 CVID patients, four had hepatic neoplasms. However, liver cancer was the fourth most common cause of cancer-related death in this cohort, accounting for 5.1% of deaths. Since the liver is a secondary lymphoid organ, it is a frequent extranodal site

for non-Hodgkin lymphoma and metastases from gastrointestinal adenocarcinomas. Therefore, liver evaluation is of particular importance in oncological surveillance to exclude both primary and secondary neoplasms (18).

The association between CVID and autoimmunity was demonstrated in several studies, affecting about 30% of patients with this diagnosis. Autoimmune manifestations include liver involvement, particularly autoimmune hepatitis, a chronic inflammatory condition of the liver occurring when the immune system attacks the liver's own cells. Although uncommon, it is a serious complication in adult patients with CVID, potentially leading to early cirrhosis, ascites and hepatocellular carcinoma. The etiology of autoimmune hepatitis remains undefined; however, viral infections and certain drugs may act as triggers (28).

Another rare condition to consider is hepatic peliosis, characterized by cavities filled with blood in the hepatic parenchyma, giving it a black-blue coloration due to the dilation of hepatic sinusoids. Although described in patients with secondary immunodeficiencies, it should serve as a red flag for excluding secondary causes. Its diagnosis is confirmed through histological liver analysis (28). Angulo *et al*. reported a case of hepatic peliosis in a patient with CVID (29).

Diagnostic approach

Currently, a standardized diagnostic approach for liver disease in patients with CVID has not been established (31). Some studies consider the diagnosis of liver involvement based on imaging signs suggestive of chronic parenchymal pathology (except for lipid infiltration), while others rely on the presence of hepatic stiffness measurements identified by transient elastography (TE) (30). Hepatic involvement can be defined as impairment of liver function or portal hemodynamics, which can be assessed through various approaches, including clinical, biochemical, imaging, and histological studies (16).

The presence of hepatomegaly and structural hepatic alterations should be closely monitored in CVID patients, as these changes may indicate advanced complications or the need for specific therapeutic interventions. Early diagnosis enables a more immediate and targeted therapeutic approach, including management of exacerbations (18).

The evaluation of liver function involves complete blood count, liver function markers, and coagulation tests (18). Approximately 40% of CVID patients show liver function abnormalities, typically with normal bilirubin levels, with the cholestatic pattern being the most common (4). In addition to elevated ALP, other parameters that may be increased include transaminases (AST and ALT), GGT, activated partial thromboplastin time (aPTT) and prothrombin time (PT), while albumin and fibrinogen levels may be decreased (15). Screening for hepatitis B (HBV) and HCV should include both serological testing and nucleic acid amplification assays (HBV DNA and HCV RNA), as antibody-based tests may be unreliable in patients with CVID due to impaired humoral responses and potential interference from immunoglobulin replacement therapy (21,27). Imaging studies, including ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen are valuable for detecting structural changes in the liver. These modalities can also identify signs of NRH, PH, liver cirrhosis, as well as esophageal varices during endoscopy (15). Additionally, they are essential for evaluating hepatosplenomegaly and screening for primary or secondary neoplastic involvement. Ultrasound is particularly advantageous due to the absence of radiation, making it an appropriate choice for CVID patients who are at increased risk of hematologic and solid organ neoplasms. Therefore, doppler ultrasound is recommended as the first-line imaging study for all CVID patients (18). However, its limitations must be considered, since the detection of PH and/or splenomegaly only occurs in more advanced stages of the disease (12).

Transient elastography (TE) is a crucial complementary tool for patients with liver involvement, as it estimates the degree of hepatic fibrosis. Current evidence shows that TE values correlate with levels of ALP and GGT, splenic diameter and blood count parameters. TE evaluation, along with doppler ultrasound, should be performed

annually, even in asymptomatic patients (18). Vibration-controlled elastography assesses liver stiffness and is validated for chronic viral hepatitis to detect cirrhosis and stratify the risk of PH and varices. It is particularly useful for evaluating CVID patients with lymphoid proliferation manifestations and enteropathy (12).

According to current recommendations, patients with multiorgan pathology, elevated GGT and a splenic diameter greater than 16 cm should undergo annual or biennial liver elastography and upper gastrointestinal endoscopy to screen for PH and secondary complications, along with annual or semiannual abdominal ultrasound (24).

Liver biopsy should be considered in patients with persistent, unexplained elevation of liver enzymes exceeding twice the upper normal limit for more than six months. This indication is further reinforced by the presence of pathological liver stiffness values and/or inconclusive imaging findings. Biopsy helps to determine the diagnosis and assess the stage of liver injury. Histologically, liver involvement in CVID is characterized by mild nonspecific lobular and portal hepatitis, lymphocytic infiltration without plasma cells, granulomas, fibrosis, macrovesicular steatosis, biliary duct neogenesis and, less commonly, findings compatible with primary PBC (7,18). Histopathological alterations consistent with NRH have been observed in patients undergoing biopsy for changes in liver function parameters, even when imaging studies are normal (18).

In CVID patients, percutaneous liver biopsy may be complicated by thrombocytopenia and coagulation abnormalities, increasing the risk of bleeding. Therefore, it is generally reserved for patients with platelet counts above 50×10^9/L and without significant PH (31). In cases of thrombocytopenia or suspected PH, transjugular liver biopsy should be considered, as it offers a safer alternative and allows concomitant assessment of portal pressure (17,24).

NRH in CVID patients most commonly presents with elevated ALP levels without increased bilirubin or PH and is associated with reduced survival (11). Its diagnosis requires histological confirmation through liver biopsy, which reveals intra-sinusoidal inflammatory cell infiltrates, including CD3+, CD4+ and CD8+ T cells, and portal venous endotheliitis with few B cells. Chronic CD8+ infiltration contributes to increased interferon-gamma production, which correlates with disease severity (6,15).

Some NRH features can be detected on imaging prior to histological confirmation (18). Abdominal CT often identifies multiple nodules with enhancement in the arterial phase or masses that are iso- or slightly hyperintense in the portovenous and late phases, without rapid "washout." Hepatic elastography also plays a role in evaluating these patients (6).

In a cross-sectional study by Di Giacomo *et al.*, 18 CVID patients were assessed with TE and there was significantly higher stiffness in those with NRH. Hepatic resistance significantly correlated with clinical parameters of PH, including an increase in the hepatic venous pressure gradient, an enlarged longitudinal splenic diameter, the presence of varices and peripheral edema. Elevation in hepatic stiffness should raise suspicion for NRH (12).

INCPH is a diagnosis of exclusion, requiring criteria outlined in Table 2 (32). The best marker for INCPH on abdominal ultrasound is a significant increase in splenic diameter, reported in more than 25% of CVID patients. However, this alteration can be secondary to both PH and lymphoproliferation, so it does not represent a specific marker for PH. Nonetheless, a spleen diameter greater than 16 cm strongly correlates with PH. TE plays a key role in detecting PH, with values greater than 20 kPa often associated with clinically significant PH (23).

Regarding serum biomarkers of liver fibrosis and collagen formation (Pro-C3, Pro-C4, and Pro-C6), only Pro-C4 and Pro-C6 were elevated in CVID patients with PH, reflecting reduced basement membrane (Pro-C4) and interstitial microfilament (Pro-C6) synthesis without significant collagen deposition (Pro-C3). These data align with the absence of significant fibrotic extracellular matrix in liver biopsies from these patients (24).

Table 2. Diagnostic criteria for idiopathic non-cirrhotic portal hypertension (INCPH). Adapted from (28).

Diagnostic criteria for non-cirrhotic portal hypertension Induced by Common Variable Immunodeficiency*
1) Clinical signs of portal hypertension (any of the following**) – Splenomegaly/splenic hyperfunction – Esophageal varices – Ascites (non-malignant) – Minimally elevated hepatic venous pressure gradient – Portal-venous collateral circulation
2) Exclusion of cirrhosis in liver biopsy
3) Exclusion of chronic liver disease causing cirrhosis or non-cirrhotic portal hypertension*** – Chronic viral hepatitis B/C – Non-alcoholic steatohepatitis/alcoholic steatohepatitis – Autoimmune hepatitis – Hereditary hemochromatosis – Wilson's disease – Primary biliary cholangitis
4) Exclusion of conditions that cause non-cirrhotic portal hypertension – Congenital hepatic fibrosis – Sarcoidosis – Schistosomiasis
5) Patent portal and hepatic veins (doppler ultrasound or computed tomography)

* All criteria must be present for the diagnosis of idiopathic non-cirrhotic portal hypertension.
** Splenomegaly must be accompanied by other signs of portal hypertension to meet this criterion.
*** Chronic liver disease must be excluded due to the possibility of under-staging of advanced fibrosis in the liver biopsy.

Histological changes associated with INCPH are not pathognomonic and include obliterative portal venopathy, portal triad hypoplasia, phlebosclerosis, portal and hepatoportal sclerosis, sinusoidal dilation, aberrant vessels, perisinusoidal fibrosis and NRH (11).

In suspected autoimmune hepatitis, testing for smooth muscle and anti-liver/kidney microsomal type 1 antibodies can be useful. However, the decreased production of antibodies in CVID reduces diagnostic accuracy (27). This limitation also applies to PBC and viral hepatitis, as disease-specific antibodies, including anti-mitochondrial antibodies, anti-HCV and HBV surface antibodies, may be decreased or undetectable in this population. Therefore, autoimmune hepatitis, PBC and viral hepatitis should still be considered even in the presence of negative serological results, and liver biopsy may be required to establish a definitive diagnosis. In suspected viral hepatitis, molecular testing (HBV DNA and HCV RNA) is essential to avoid false-negative serological findings (21,27). Overall, the diagnostic approach to liver involvement in CVID is complex, and no universal algorithm currently exists. Baumert *et al.* proposed a diagnostic algorithm illustrated in Figure 1.

Therapeutic Approach

The therapeutic approach for CVID patients with hepatic involvement requires a comprehensive strategy addressing both the treatment of immunodeficiency and the specific management of hepatic complications. However, to date, there are no standardized clinical guidelines for appropriate treatment.

Immunoglobulin replacement therapy plays a crucial role in preventing infections but does not appear to influence the development of non-infectious complications (6). Currently, no specific therapy exists for hepatic involvement in CVID, and liver transplantation is considered a therapeutic option only in selected cases, such as cirrhosis, end-stage chronic liver disease and HPS (7,11,12,16,23). It remains the only therapeutic approach with potential to prolong survival, although the 3–5 year survival rate is approximately 55%, with multiple associated complications, including frequent infections, recurrence of disease in the transplanted graft and the development of *de novo* neoplasms (17,21). In cases of NRH, autoimmune hepatitis or granulomatous hepatitis, treatment generally involves corticosteroids and immunomodulatory drugs, such as azathioprine, 6-thioguanine and 6-mercaptopurine (31). Regarding autoimmune hepatitis, immunosuppressive therapy with cyclosporine A has been effective in reversing liver dysfunction (27). When NRH

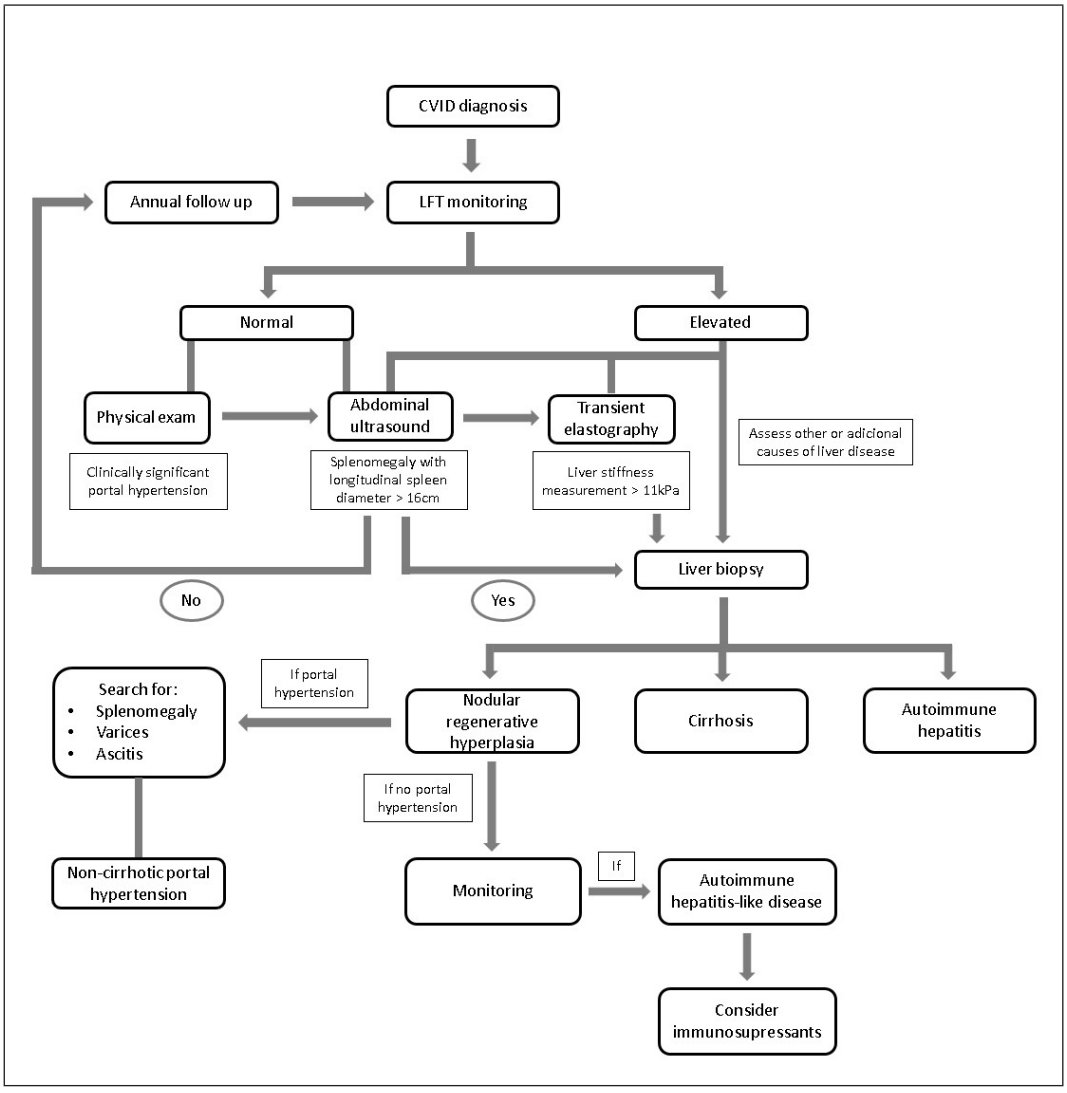

Figure 1. Diagnostic algorithm for hepatic manifestations in common variable immunodeficiency (CVID) . Adapted from (4). LFT, liver function tests

is linked to a prothrombotic condition, anticoagulation therapy is recommended. For patients presenting with PH, standard management strategies may include non-selective beta-blockers such as propranolol or carvedilol, transjugular intrahepatic portosystemic shunt (TIPS) placement and endoscopic variceal ligation to control bleeding (31).

Ursodeoxycholic acid may be indicated when biliary injury is histologically confirmed (15).

Since there is no curative treatment for INCPH, management focuses on preventing and treating complications (11,20).

For patients developing HPS, liver transplantation may be considered as an option, contributing to the reversal of hypoxia, although infection and rejection rates remain high (27,33).

Despite the therapeutic options currently available, patients with CVID exhibit reduced life expectancy. In

the study performed by Bez *et al.*, involving a cohort of 497 patients with CVID, 57 deaths were identified. CVID patients exhibiting the complicated phenotype (CVIDc), defined by the presence of any noninfectious manifestations beyond splenomegaly, had a median survival of 37 years from diagnosis. Mortality among CVIDc patients was predominantly attributable to infections (37%) and neoplasms (27%). Among cancer-related deaths, gastric carcinoma was the most frequent (7.8%). Severe enteropathy, hepatopathy and interstitial lung disease typically preceded death by 3 to 5 years and were strongly associated with premature mortality. Notably, the presence of severe enteropathy and hepatopathy three years prior to death emerged as the most reliable prognostic indicators, underscoring their potential utility for risk stratification and the management of CVID patients. (34)

In CVID patients with liver involvement, regular liver function testing every 2-6 months is required, together with yearly ultrasound and TE to monitor progression and estimate the degree of fibrosis (31).

CONCLUSION

Liver involvement is observed in a significant proportion of patients with CVID and encompasses a variety of manifestations leading to abnormal liver function. The increasing number of patients diagnosed late with progressive liver disease highlights the importance of early recognition and appropriate management of hepatic complications.

Comprehensive evaluation, including a detailed clinical history, laboratory assessment and imaging studies, is essential for identifying hepatic involvement in CVID patients. Therefore, a multidisciplinary approach involving specialists in allergy/immunology, internal medicine and hepatology is crucial for accurate diagnosis and optimal therapeutic management.

In summary, liver disease in CVID patients requires regular monitoring, as hepatic impairment is associated with significant morbidity and mortality. Regular monitoring and early intervention are key factors to improve patient outcomes.

Acronyms

ALP – alkaline phosphatase;
ALT – alanine aminotransferase;
aPTT – activated partial thromboplastin time;
AST – aspartate aminotransferase;
CT – computed tomography;
CVID – common variable immunodeficiency;
CVIDc – complicated phenotype CVID;
IEI – inborn errors of immunity;
INCPH – idiopathic non-cirrhotic portal hypertension;
IUIS – International Union of Immunological Societies;
ESID – European Society for Immunodeficiencies;
HBV – hepatitis B virus;
HCV – hepatitis C virus;
HPS – hepatopulmonary syndrome;
HR – hazard ratio;
MRI – magnetic resonance imaging;
NRH – nodular regenerative hyperplasia;
PBC – primary biliary cholangitis;
PH – portal hypertension;
PID – primary immunodeficiencies;
PT – prothrombin time;
TE – transient elastography;
TIPS – transjugular intrahepatic portosystemic shunt.

Conflicts of interest

The authors disclose they have no conflicts of interest.

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