Review

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Management of liver disease and portal hypertension in common variable immunodeficiency (CVID)

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Summary

Patients with common variable immunodeficiency (CVID) frequently develop liver disease and associated complications, which represent an increasingly prevalent unmet medical need. The main hepatic manifestation of CVID is nodular regenerative hyperplasia (NRH), resulting in non-cirrhotic portal hypertension (NCPH). Liver disease is often underdiagnosed, leading to poor outcomes and decreased survival. The increasing numbers of patients with CVID who are diagnosed late with progressive liver disease underscores the importance of appropriate clinical management and treatment of liver complications. At the same time, specific guidelines for the clinical management of CVID-related liver disease are still lacking. Here, we review the epidemiology of CVID-related liver disease, reveal new insights into NRH and NCPH biology and highlight recently uncovered opportunities for NCPH diagnostics in CVID. Finally, we focus on current management of liver disease, portal hypertension and its complications – the key challenge in patients with CVID. Specifically, we review recent data regarding the role of transjugular intrahepatic portosystemic shunt and liver transplantation in clinical management. The role for anticoagulants and immunosuppressants targeting the pathogenesis of NRH will also be discussed. We propose an updated algorithm for the diagnostic work-up and treatment of NCPH in CVID. Finally, we consider future needs and therapeutic opportunities for CVID-related liver disease.

Keywords: nodular regenerative hyperplasia; non-cirrhotic portal hypertension; liver transplantation; TIPS; algorithm; autoimmune hepatitis; gut-liver axis; CVID

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Clinical course and epidemiology

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder (PID) characterized by hypogammaglobulinemia[1] as a possible result of dysfunctional B cell maturation.[2] The underlying pathogenesis remains poorly understood. CVID encompasses an array of genetic disorders rather than a single disease.[3,4] The highest prevalence is observed in Northern and Western countries, particularly the United States,[5–8] with incidences ranging between 1:10,000 and 1:50,000.[9,10] The median age of onset ranges from 20–45 years.[11–14] CVID is most prevalent amongst PIDs in adults.[8,10,15] CVID is clinically heterogenous with manifestations in various systems including respiratory infections,[16] lymphoproliferation and malignancy,[17] autoimmunity,[18] allergic disease and asthma,[6] as well as disease of the liver and gut.[19,20] Diagnosis is challenging and often delayed, resulting in organ damage.[21] Diagnostic hallmarks of CVID are low IgG, IgA and/or IgM serum levels, inadequate production of specific antibodies, and exclusion of other causes of hypogammaglobulinemia.[1,22,23] Differential diagnosis includes several other PIDs with similar clinical presentation.[20] Primary treatment encompasses lifelong replacement of immunoglobulins. Hematopoietic stem cell transplantation (HSCT) can be performed on a case-by-case basis but carries a very high risk of infectious complications.[24] Adjunctive treatments include antibiotics for infection management[25] and immunosuppressants for specific patients displaying autoimmune manifestations.[26] An overall mortality rate of 19.6% has been reported in patients with CVID.[14]

The prevalence of liver involvement in CVID varies and depends on the diagnostic criteria being applied. A prevalence of 9% to 79% was described in a recent meta-analysis.[4] The prevalence depends on the definition of liver involvement, which can be assessed through laboratory parameters, clinical appearance, imaging or histopathological criteria. A recently published cohort of patients with CVID[27] revealed that 46 out of 141 patients (33%) presented with liver disease. In this study, "liver disease" was defined by "imaging signs of chronic parenchymal liver disease, except fatty infiltration". In one study,[4] a prevalence of liver disease of 33.8% was observed in 77 adults with CVID. Liver involvement was defined by liver stiffness on transient elastography (TE). When using histopathological criteria to define liver involvement, the prevalence seems to be lower: a retrospective study of 205 patients with CVID by Farmer *et al.*[28] reported a prevalence of 9.3%.

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Liver pathology in patients with CVID includes granuloma, immune hepatitis, patchy sinusoidal fibrosis/lymphocytosis and nodular regenerative hyperplasia (NRH), which is the most common manifestation (Fig. 1).[29–31,22] NRH is associated with porto-sinusoidal vascular disease (PSVD) and non-cirrhotic portal hypertension (NCPH). Predominant clinical features of NCPH in one CVID cohort[27] were splenomegaly (82.6%), oesophageal varices (39.1%), gastric varices (19.6%) and hepatomegaly (13%). Liver disease-associated complications include variceal bleeding, ascites and rarely hepatopulmonary syndrome.[23] Outside CVID, patients with NCPH frequently present with extrahepatic portal vein thrombosis[32,33] however, data on CVID are limited. Liver involvement in patients with CVID is a key determinant of outcome and prognosis: mortality is higher in patients with liver involvement than in those without[34,14,23] NRH and NCPH in particular are associated with reduced survival in patients with CVID.[34] The increasing numbers of those with belatedly diagnosed CVID and advanced liver disease underscores the importance of optimising clinical management and treatment of NCPH-related complications. However, relevant clinical guidelines are lacking. Hence, there is an urgent need to improve our understanding of the underlying biology of CVID and thereby develop improved diagnostic and therapeutic approaches.

Key points

- Mortality of patients with CVID and liver involvement (nodular regenerative hyperplasia and non-cirrhotic portal hypertension in particular) is higher than in those without.
- Management of patients with CVID requires a multidisciplinary approach involving experts specialized in vascular liver diseases and CVID.
- The initial work-up includes liver function tests and imaging with abdominal ultrasound, which should be followed by transient elastography of the liver to detect (early) portal hypertension.
- Patients with a longitudinal spleen diameter ≥16 cm and liver stiffness measurement values ≥11 kPa should undergo liver biopsy.
- Liver biopsy serves as the cornerstone of diagnosis, enabling identification of the underlying pathology and hence evaluation of personalised therapeutic options.
- Immunosuppressants may be beneficial for patients with autoimmune hepatitis (like) disease. However, they should be administered with caution.
- Standard therapeutic approaches for portal hypertension, such as TIPS, improve NCPH significantly, but unfortunately are associated with a high rate of infectious complications that are linked with poor prognosis.
- Emerging therapeutic approaches that target the underlying disease, such as anticoagulants or faecal microbiota transplant, should be further investigated in clinical trials.

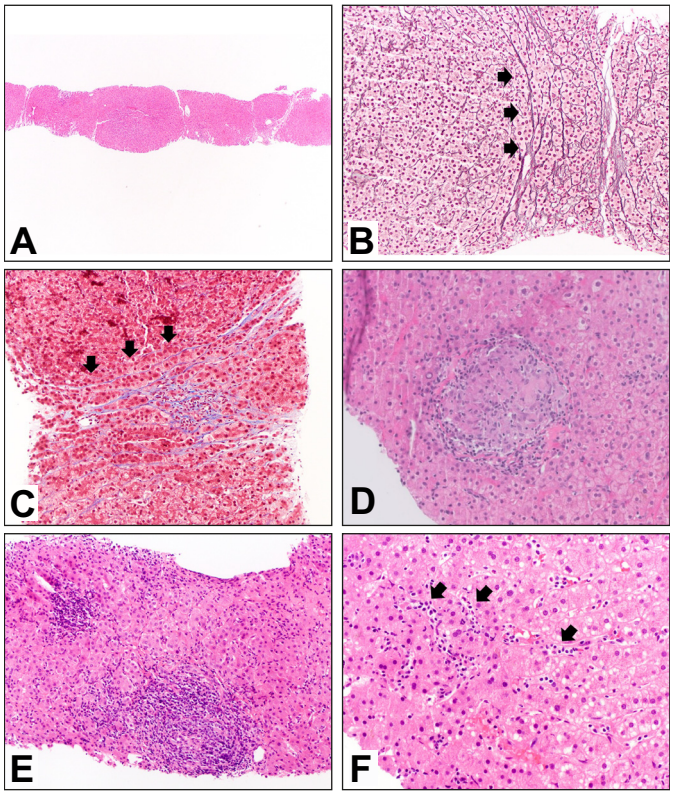

Fig. 1. Histology of CVID. The most common histologic manifestation of CVID is nodular regenerative hyperplasia, which is recognized on routine H&E staining as nodular liver parenchyma in the absence of established bands of fibrosis (A). A reticulin stain confirms the parenchymal nodularity by highlighting mildly hyperplastic trabecular plates (B, left of arrows) and mildly atrophic trabecular plates (B, right of arrows). A trichrome stain highlights patchy sinusoidal fibrosis (arrows) without established fibrous septae (C). Other less common histologic manifestations of CVID include well-formed, non-necrotizing parenchymal granulomas (D); dense mononuclear portal inflammation with interface activity, consistent with an immune hepatitis (E); and patchy sinusoidal lymphocytosis (F, arrows). CVID, common variable immunodeficiency.

Disease biology of NRH

Definition of NRH and PSVD

NRH is largely a histopathological diagnosis defined by regenerative plaques in an area of ≥2 hepatocytes with intervening areas of thinned trabeculae and atrophic hepatocytes, in the absence of bridging fibrosis or established cirrhosis;[35,36] it appears to be a secondary complication.[37] NRH is also referred to as porto-sinusoidal vascular disease (PSVD), which aims to describe histological alterations of liver tissue in patients with NCPH.[35] Importantly, this definition emphasizes the absence of cirrhosis as a diagnostic criterion.[38] While the precise aetiology of NRH remains largely unknown, several new concepts for NRH disease biology have recently emerged.

Suspected mechanisms leading to NRH and PSVD

Thrombosis. Pathology classifies NRH and associated NCPH as a microvascular disorder of the liver.[31,39,40] The nodular regenerative pattern of hepatocytes is suspected to be an exaggerated response to impaired blood flow.[41] In one cohort of patients with NRH,[42] portal vein obliteration, paraportal shunts, atretic portal tracts, and dilated thin portal venules were found in several cases, implicating obliterative portal venopathy as an underlying mechanism. The same study also observed a phenotypic shift of sinusoidal endothelial cells toward CD34 expression and thus capillarization of periportal sinusoids, reflecting higher blood flow and hypertrophy of acinar hepatocytes, which might reflect compensatory blood flow caused by obliterative portal venopathy. In addition, prothrombotic states and a higher incidence of portal vein thrombosis have previously been associated with NCPH,[43,44] suggesting (micro)thrombosis as a possible driver of

NCPH. Histopathological thrombosis found in medium and small portal vein branches supports this hypothesis.[45]

Lymphocytic infiltration. Lymphocytic infiltration has been suggested as a possible contributor to NRH pathogenesis: one study[27] investigated 11 liver biopsies from patients with NRH and NCPH in the context of CVID. Mild to moderate periportal hepatic lymphocytosis was observed in eight cases. Furthermore, electron microscopy showed mild to moderate lymphocytic infiltration of the liver, suggesting lymphocyte-mediated cytotoxicity as a possible driver of liver injury in NRH in the context of CVID. Interestingly, in patients with NRH without CVID, $CD8^+$ T cells were observed in liver sinusoids. Furthermore, residual cytotoxic T cells were found in the area of apoptotic endothelial cells[29,46] rather than hepatocytes.[27] The cause of this observation remains unclear – there could be a link to the dysregulation of the immune system in CVID, as lymphocytic infiltration is a common phenomenon in a variety of organs.[47,48] These findings imply that chronic cytotoxic T-cell infiltration of the sinusoidal endothelium may be a cause of NRH. In turn, this may account for altered blood flow through the portal system, which could reduce hepatic perfusion.

Microbial translocation. The observed lymphocytic infiltration of the liver could be the result of an impaired gut-liver axis. Outside CVID it is well known that the immune system interacts with bacteria of the intestinal microbiome, which triggers an immune response.[49,50] In this context, microbial dysbiosis describes an increase of pro-inflammatory bacteria, in turn promoting dysregulation of the immune system.[51] As the microbiome plays a crucial role in maintaining the physical barrier function of the gut,[52] dysbiosis and thus reduced microbial diversity, enables bacteria to infiltrate the gut through intracellular and paracellular pathways.[52,53] This can lead to microbial translocation, which is defined as the movement of microorganisms and endotoxins to extraintestinal regions,[54–56] including the hepatic portal circulation.[57,58] Microbial translocation can be assessed using plasma lipopolysaccharide (LPS) as a biomarker.[59]

Although recent literature explicitly examining injury of the gut barrier in patients with CVID is limited,[60] an association between enteropathy and liver disease has been elegantly described in two studies.[30,61] Dysbiosis, reduced microbial diversity and elevated plasma LPS levels inversely associated with reduced microbial diversity have been observed in patients with CVID.[62] The prevalence of intraepithelial lymphocytosis in the duodenum of patients with CVID and gastrointestinal involvement ranges from 17.1% to 75.6%.[63–65] Intraepithelial lymphocytes in CVID-related enteropathy were mostly $CD8^+$.[64]

Limited data in patients with CVID, including similar histopathological findings in hepatic sinusoids and gut epithelium implicate lymphocytic infiltration as a possible response to microbial translocation (Fig. 2A). However, further examination of the gut-liver axis, including gut-barrier function, in patients with CVID is required to confirm the proposed hypothesis.

Autoimmunity. Fuss *et al.*[31] reported findings of autoimmune hepatitis (AIH)-like liver injury. While histopathological criteria of NRH such as nodular regeneration and perisinusoidal fibrosis were similar to the findings of Lima *et al.*, Fuss *et al.* additionally observed portal inflammatory infiltration and bridging necrosis, with the absence of plasma cells, accompanied by a more severe clinical presentation with hepatitis and an alteration of excretory liver function.[31] Given the simultaneous presentation of the nodular regenerative tissue with histopathological and clinical features of AIH in patients with CVID, the authors suggested a unique CVID associated AIH-like hepatitis (Fig. 2B). Moreover, Fuss *et al.* divided patients with NRH into three categories based on clinical appearance: NRH progressing or not progressing to NCPH, and patients with both NRH and AIH characterized by significant hepatic dysfunction, which was referred to as

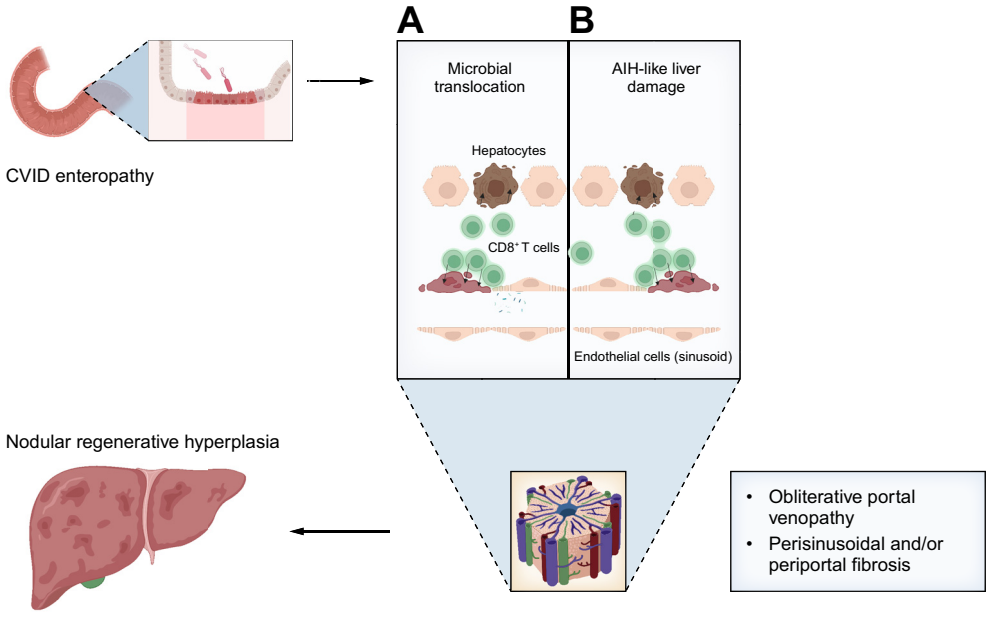

Fig. 2. Model of NRH pathogenesis in patients with CVID. (A) Microbial translocation in patients with CVID and enteropathy possibly leading to lymphocytic infiltration of hepatocytes or sinusoidal endothelial cells as a reaction to pathogens. (B) Autoimmune-like T-cell infiltration of hepatocytes or sinusoidal endothelial cells leading to liver damage/apoptosis. Figure adapted from Pecoraro *et al.*[4] AIH, autoimmune hepatitis; CVID, common variable immunodeficiency; NRH, nodular regenerative hyperplasia.

"severe". Interestingly, $CD8^+/CD3^+$ T-cell infiltration was observed in most biopsies as well, accompanied by elevated IFN-gamma production in biopsies with severe NRH. Furthermore, increased granzyme B expression in $CD8^+$ T cells is associated with autoimmunity in CVID.[66] This has been observed in patients with NRH without CVID[46] and should be further investigated. In addition to lymphocyte-mediated cytotoxicity, (seronegative) autoimmunity constitutes another possible mechanism of liver injury in CVID (Fig. 2). This latter hypothesis is supported by two case reports which show seronegative AIH accompanied by lymphocytic infiltration and plasma cells in patients with CVID.[67,68] Liver test elevations were much more pronounced than in patients with CVID and NRH (Table 1).

Although liver disease and NRH have been linked with CVID-related enteropathy,[30,61,69] it remains to be fully established whether $CD8^+/CD3^+$ lymphocytic infiltration is attributable to microbial translocation or autoimmunity. Both mechanisms could contribute to NRH pathogenesis (Fig. 2). The possible presence of AIH should be considered in view of its therapeutic implications.

Diagnostic work-up of CVID-induced liver disease

Laboratory parameters and LFTs

Evaluation of liver function tests (LFTs) plays a key role in the initial diagnosis and as a screening parameter for liver disease. However, not all patients with CVID and NRH show changes in laboratory parameters; some even present with normal LFTs.

In a cohort of 46 patients with CVID and NCPH,[27] 10.9% displayed normal LFTs with thrombocytopenia; an additional 13% had normal LFTs and platelet count. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were mildly increased in about 30%, whereas alkaline phosphatase (ALP) was increased in 60% of patients. Fuss *et al.*[31] observed an increase in ALP of about 2x the upper limit of normal (ULN) and an AST/ALT elevation of 2-3x the ULN a mean of 7.8 years after the diagnosis of CVID. Laboratory changes were not observed in all patients investigated. In two case reports[67,68] of seronegative AIH in CVID, AST and ALT were much more severely elevated (ALT and AST of 31x and 47x the ULN, respectively, and total bilirubin of 8x the ULN[67] [Table 1]). The elevation of serum IgG[70] typically seen in AIH is lacking in CVID, likely attributable to the characteristic immunoglobulin deficiency. Laboratory identification of AIH can thus be challenging and must not be overlooked.

For initial diagnostic workup, we suggest LFTs including AST/ALT, ALP, total bilirubin and clotting profile. A marked increase of AST/ALT should prompt suspicion for underlying autoimmune disease (Table 1).[27,31,67,68] LFTs alone are not reliable, since normal laboratory parameters have been observed even in late-stage liver disease.[27] Imaging should also be performed to avoid overlooking liver injury in patients with normal LFTs. Laboratory parameters of patients presenting with normal LFTs and normal imaging should be monitored annually.[34] Severe LFT elevation warrants liver biopsy to rule out (seronegative) AIH (Fig. 4).

Imaging

Abdominal ultrasound, TE and MRI can detect structural, anatomical, and haemodynamic changes of the liver-spleen axis. With portal hypertension presenting as the main clinical complication, abdominal ultrasound and TE should be used early in the initial patient work-up. Splenomegaly was the most common clinical presentation of CVID/NRH/NCPH observed in multiple studies.[27,71] Globig *et al.*[71] observed that a longitudinal spleen diameter of more than 16 cm was highly associated with portal hypertension. Not all patients with splenomegaly presented with impaired LFTs,[27] underscoring the importance of imaging. However, splenomegaly could also result from lymphoproliferation rather than liver disease. Ultrasound can be extended using TE: one study[71] observed increased liver stiffness measurements (LSM) in all patients with portal hypertension, with 11.2 kPa as a cut-off. Furthermore, the longitudinal spleen diameter and serum ALP were significantly correlated with LSM values.[61] Spleen stiffness measurement (SSM) is an emerging tool in the diagnostic work-up of NCPH.[72] Although the literature regarding its use in NCPH remains limited, two studies have demonstrated increased SSM in patients with PSVD without CVID, using shear-wave elastography.[73,74] These observations suggest that SSM in conjunction with LSM is useful in the diagnostic work-up of PSVD.[73,75] However, detailed data regarding SSM in CVID are lacking. Considering the high prevalence of NCPH and its association with lower survival,[34] the diagnostic efficacy of SSM in patients with CVID should be further investigated. CT imaging is able to detect enlarged collateral veins in patients with CVID and portal hypertension,[31] and to uncover intrahepatic vascular irregularities specifically in peripheral portal vein branches (present in obliterative portal venopathy).[76]

Recent literature supports initial abdominal ultrasound to evaluate the spleen diameter, which should be followed by TE of the liver. For patients with a longitudinal spleen diameter of more than 16 cm as well as increased LSM values, semi-annual ultrasound follow-up as well as TE every 1-2 years has been recommended to detect (early) portal hypertension;[71] we

Table 1. Analysis of LFT elevations in patients with CVID (with AIH *vs.* NCPH and NRH).

CVID cohort	Elevated AST	Elevated ALT	Elevated ALP	Thrombocytopenia	Total bilirubin increased	INR increased	Diagnosis
Lima *et al.* 2022;[27] n = 46	In 34.8%: 1.2–2.8 × ULN	In 30.4%: 1.1–3.1 × ULN	In 60.9 %: 1.1–5.1 × ULN	In 63.0%	In 21.7%	In 4.3%	NCPH and NRH
Fuss *et al.* 2013;[31] n = 14	2-3x ULN	2-3x ULN	2x ULN	In 64.3%	In 28.6%: increase 1.5-2.5 years after rise of ALP	In 42.8%: increase 1.5-2.5 years after rise of ALP	NCPH and NRH
Myneedu *et al.*[67] 2021; n = 1: case report	47x ULN	31x ULN	5x ULN	yes	By the time of admission: 5x ULN; After 1 month: 16x ULN	3x ULN	AIH
Pollock *et al.*[68] 2020; n = 1: case report	44x ULN	9x ULN	2x ULN	–	–	–	AIH

This table compares laboratory parameters of patients with CVID (with AIH and NRH/NCPH). Patients with AIH show much more severely elevated AST and ALT. AIH, autoimmune hepatitis; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CVID, common variable immunodeficiency; INR, international normalised ratio; NCPH, non-cirrhotic portal hypertension; NRH, nodular regenerative hyperplasia; ULN, upper limit of normal.

suggest additional liver biopsy in these patients. Patients with CVID without liver pathology on imaging should be routinely monitored annually by abdominal ultrasound[71] (Fig. 4).

Liver biopsy and NRH

Biopsy of the liver serves as the gold standard for the diagnosis of NRH. The histopathological criteria for diagnosis of NRH were first proposed in 1990[36] and revised in 2015.[40] The revised criteria include "nodular regenerative hyperplasia of the liver characterized by the focal or diffuse appearance of hepatocellular nodule(s) less than 3 mm in diameter consisting of a central part of enlarged hepatocytes and/or thickened liver cell plates with a rim of smaller hepatocytes and/or thinner liver cell plates with compression of the sinuses in the periphery where perisinusoidal but not septal fibrosis may occur. The nodules need to be distinct on both H&E and reticulin staining".[40]

However, interobserver agreement remains poor even after reassessment with modified criteria. Therefore, adherence to quality criteria for liver biopsy is crucial, including obtaining a specimen that is ≥20 mm in length, containing ≥10 portal tracts, and ensuring it is not excessively fragmented as suggested by De Gottardi *et al.*[35] Interpretation should be conducted by an expert pathologist. In 2020, the European Association for Vascular Liver Disease (VALDIG) proposed new criteria for the diagnosis of PSVD.[35] A patient with CVID with the specific histologic absence of cirrhosis and the presence of NRH meets the diagnostic criteria for PSVD, which affects treatment approaches. Given its accuracy, liver biopsy serves as the cornerstone of diagnosis, making it an essential component of the diagnostic work-up to evaluate personalised therapeutic options (Fig. 4).

Current treatment options in CVID-related liver disease

The most common hepatic manifestation of CVID is NRH, which is associated with NCPH.[22,29–31] There are two therapeutic concepts for NRH and NCPH: (1) targeting underlying drivers to prevent progression of the disease; (2) symptomatic treatment of NCPH (Fig. 3).

Therapeutic concepts targeting underlying disease biology

Immunosuppressants

Lymphocytic T-cell infiltration of sinusoidal endothelial cells as well as hepatocytes has been observed in patients with CVID and is suggested to contribute to NRH progression.[27,31,69] Moreover, 20-25% of patients with CVID exhibit autoimmune manifestations,[26,77,78] indicating a possible role for immunosuppressive therapy in this disorder. In one report,[31] two out of five patients with AIH-like liver injury were treated with prednisone and azathioprine (AZA). However, both patients died of progressive liver disease. In contrast, a young patient with AIH-like disease who was treated with steroids and 6-mercaptopurine (6-MP) experienced successful control of liver disease. The authors suggest that the first two patients were treated at an advanced stage that had become non-responsive, whereas treatment of a younger patient resulted in regression of liver disease. In a case report of seronegative AIH in CVID,[67] a patient with highly increased LFTs and total bilirubin was placed on prednisone, which was tapered over a course of 6 months, with AZA applied 3 months into the taper. This led to a significant improvement of LFTs.

Interestingly, thiopurines, specifically 6-thioguanine (6-TG), AZA and 6-MP, have been associated with the occurrence of NRH and portal hypertension. This has mainly been observed in patients without CVID with inflammatory bowel disease.[79,80] Application of high-dose 6-TG was associated with a higher incidence of NRH compared to low-dose 6-TG or AZA,[79,81] suggesting that 6-TG toxicity is dose dependent.[82] Cases of 6-MP-associated NRH are rare.[79] Data on thiopurines in CVID are limited to case reports as mentioned above.

These data suggest that immunosuppressive treatment should be considered in selected patients with CVID and AIH-like disease or seronegative AIH as the underlying mechanism: however, due to the reported hepatotoxicity of high-dose 6-TG, we suggest treatment with low-dose 6-TG, AZA or 6-MP and/or steroids with careful monitoring. However, immunosuppressants in the general CVID population should be administered with caution as they may exacerbate the underlying

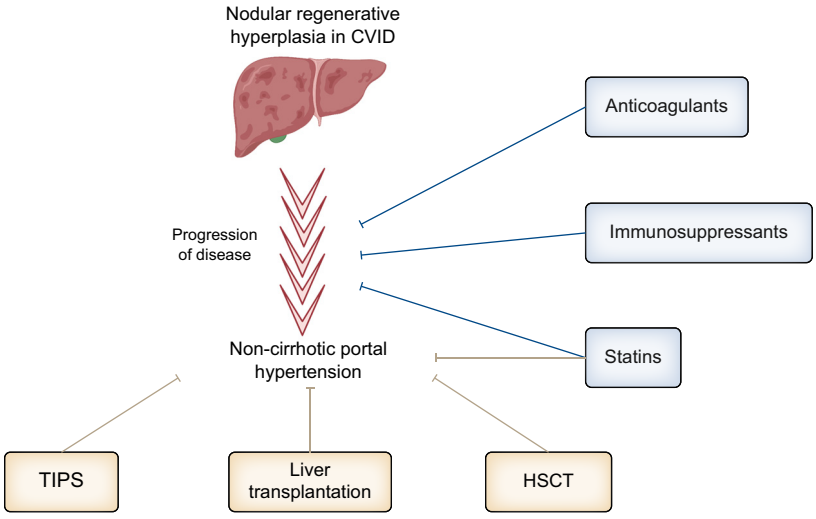

Fig. 3. Overview of different therapeutic approaches in CVID-associated NRH and NCPH. Anticoagulants and immunosuppressants aim to delay NRH progression, statins additionally target manifest NCPH. TIPS, liver transplantation and HSCT target manifest NCPH and its complications specifically. CVID, common variable immunodeficiency; HSCT, haematopoietic stem cell transplantation; NCPH, non-cirrhotic portal hypertension; NRH, nodular regenerative hyperplasia.

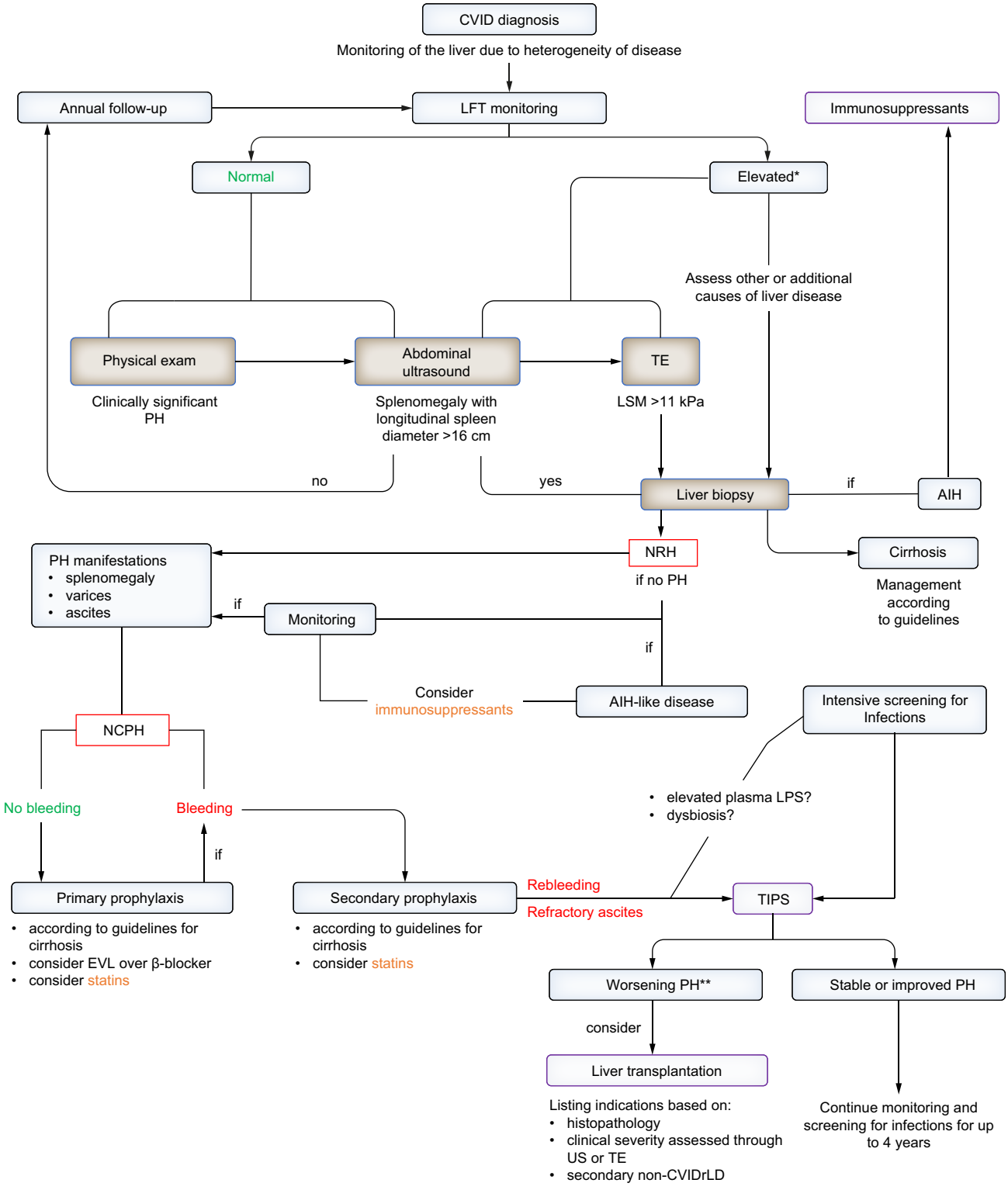

Fig. 4. Proposed algorithm for management and diagnosis of liver manifestations in CVID. Information analysed in our review were integrated into an algorithm. It includes the most recent data on diagnosis and management of the most relevant liver manifestations in CVID and aims to provide an overview. *If LFTs are severely elevated (AST/ALT >3x the ULN, TB >8x the ULN), obtain liver biopsy due to possible AIH. Consider liver biopsy for mild LFT elevations (AST/ALT <3x the ULN). **For selected patients, consider sequential liver transplantation and HSCT. AIH, autoimmune hepatitis; CVID, common variable immunodeficiency; EVL, endoscopic variceal ligation; LFTs, liver function tests; LSM, liver stiffness measurement; NCPH, non-cirrhotic portal hypertension; non-CVIDrLD, non-CVID-related liver disease; PH, portal hypertension; TB, total bilirubin; TE, transient elastography; US, ultrasound.

immunodeficiency, as seen by their contribution to the high mortality and poor prognosis of patients after liver transplantation (LT) or HSCT.[83]

Management of NCPH

Management of patients with CVID requires a multidisciplinary approach involving experts specialized in vascular liver diseases and CVID. This need becomes apparent in view of the poor prognosis and limited therapeutic options, thus underscoring the importance of a detailed analysis of management options for NCPH in patients with CVID. The first signs of portal hypertension in CVID occur 11.8 years after the diagnosis.[27] This suggests a picture of steady progression of liver injury. Consequently, immediate treatment should be started once NCPH is diagnosed. The most relevant complication of portal hypertension is variceal bleeding. The management of PSVD-associated NCPH was recently assessed in the Baveno VII consensus document.[72] However, data regarding the management of PSVD-associated portal hypertension specifically in patients with CVID have not yet been independently evaluated. Thus, the question is, do the Baveno VII consensus recommendations for NCPH apply to patients with CVID?

Therapeutic approaches for variceal bleeding encompass several strategies, including endoscopic variceal ligation (EVL) and non-selective beta-blockers (NSBBs) such as propranolol and carvedilol - the latter presenting with additional alpha-1-blocking properties that contribute to reducing portocollateral resistance.[84] Due to their ability to decrease portal pressure, both are utilized as prophylaxis in patients with portal hypertension to prevent variceal bleeding.[72]

Carvedilol demonstrated greater efficacy than propranolol in reducing hepatic venous pressure gradient (HVPG) in patients with cirrhosis and portal hypertension[85,86] and is thus recommended in the Baveno VII consensus document for patients with compensated cirrhosis.[72] Regarding the treatment and prophylaxis of varices in CVID specifically, data are not yet available. In a prospective randomized-control trial, Sarin *et al.*[87] compared EVL to drug therapy (propranolol + isosorbide mononitrate) in patients with cirrhotic portal hypertension and NCPH. In patients with NCPH, EVL therapy was shown to be more effective as primary prophylaxis than pharmacologic therapy. A similar study[88] compared the efficacy of EVL *vs.* propranolol as secondary prophylaxis, which showed no difference in outcome. Given the low number of patients, additional studies are needed. Based on the lack of specific data, treatment according to guidelines for cirrhotic portal hypertension[72] should be applied to patients with CVID as recommended in the Baveno VII consensus document. The potential benefit of EVL therapy (for primary prophylaxis) and carvedilol should be investigated in patients with CVID and NCPH.[89]

Uncontrollable variceal bleeding and refractory ascites warrant transjugular intrahepatic portosystemic shunt (TIPS) placement.[90–92] In a retrospective study, Globig *et al.*[93] collected data from a cohort of 13 patients with CVID who underwent TIPS in clinical centres in Europe and North America. NRH as an underlying liver disease was observed in nine patients. In 12 out of 13 patients TIPS significantly reduced the HVPG. Recurrent variceal bleeding was prevented in all 13 patients after TIPS, and a decrease in spleen size was observed in six patients, though physiological size was not reached. However, six of 13 patients died of sepsis (46%): one death being procedure related, the remaining five deaths occurred up to 5 years after the procedure. A recent meta-analysis[94] on infectious complications in CVID reported a prevalence of sepsis ranging from 1.2–22.2%. This finding suggests that the high prevalence of sepsis observed in this study (46%) was associated with TIPS implementation, although only one death was listed as procedure related. This is supported by data on the prevalence of septic non-procedure-related complications after TIPS implementation in patients with NCPH without CVID: in a retrospective study, Bissonnette *et al.*[95] observed an overall mortality rate of 27% within 5 years after TIPS, with 18% of deaths attributable to sepsis or multiorgan failure.

Because sepsis-related death has been observed up to 4 years after TIPS placement, the utility of antibiotic prophylaxis after TIPS is unknown: while antibiotic prophylaxis did not provide any benefit in terms of procedure-related complications in patients without CVID,[96] studies in patients with CVID are lacking. Furthermore, extrahepatic events should be taken into consideration when choosing TIPS as a therapeutic option: studies have shown that the involvement of the gut (enteropathy) is associated with higher mortality in patients with CVID.[47] Impairment of the liver-gut axis could also contribute to the high rate of sepsis after TIPS, as suggested by some.[93] The liver tissue acts as a gatekeeper between the systemic circulation and pathogens in the gut,[97,98] however, its ability to perform this role could be impaired by the portosystemic shunting that is inherent to TIPS. Additionally, microbial dysbiosis in CVID[62] and microbial translocation could further increase the risk of sepsis. These considerations underscore the need for therapeutic options that target the gut-liver axis. However, considering the small study population, more prospective data on TIPS in CVID are needed.

For progressive liver disease with treatment failure, transplantation serves as a last therapeutic option offering potential long-term survival. Because of the late recognition of hepatic manifestations of CVID and the absence of treatments targeting the underlying biology of progressive NRH/PSVD, LT remains a possible option that should be investigated. In a case series and meta-analysis, Azzu *et al.*[99] analyzed outcomes after LT in patients with CVID. Reviewing 18 cases, the authors concluded that mortality was higher in patients with CVID undergoing LT than in patients undergoing LT for other disease aetiologies. In a systematic review, Tranah *et al.*[83] also reported a high number of cases experiencing severe infections (80%) and recurrence of CVID (43%) post-transplant despite continuing immunoglobulin replacement therapy.

CVID as a primary immunological disease persists after LT, likely contributing to poor outcomes owing to the even higher risk of infection. Interestingly, patients with a secondary aetiological factor for liver disease which was non-CVID-related (*e.g.* chronic hepatitis C) performed better post-transplant (5-year post-transplant survival of 69.6% *vs.* 52.4%).[83] Aetiology of liver disease should thus be considered when listing a patient with CVID for transplantation.

Taking into account the limited data and poor prognosis associated with liver disease in CVID, a careful benefit-risk balance may help in clinical decision making: Benefits include the life-saving nature of LT, particularly in young patients.[100,101] On the other hand, risks include the persistence of the immune disturbance and a high risk of infectious complications.

Therefore, careful consideration should be given to LT in CVID. To optimize clinical management, indications for LT listing should be established in patients with CVID. Due to the genetic heterogeneity of CVID, different phenotypes and a multifactorial pathogenesis, establishing guidelines remains difficult with the limited data available. More emphasis on antibiotic prophylaxis as well as screening for opportunistic infections could improve post-LT survival. Laboratory parameters can present as unimpaired and possibly misleading due to preserved liver function.[102] Therefore, more emphasis should be placed on histopathology as well as the clinical severity of portal hypertension, which can be evaluated via ultrasound and TE.[61,71] Further, immunosuppressive drugs should be selected carefully, since AZA and 6-MP have been associated with the development of NRH post transplantation.[103,104,80,105]

An approach under clinical investigation includes combined LT and HSCT. HSCT alone has been performed in patients with CVID. Like TIPS implantation, HSCT was beneficial in patients who survived, although some patients remained dependent on immunoglobulin replacement after transplantation. However, infectious complications and severe graft *vs.* host disease contributed to a mortality rate of 52% over 2 years.[24] Moreover, patients with liver involvement experienced an even lower survival rate.[24] HSCT does not appear to correct the underlying immune defect in all patients and could therefore aggravate the condition because of the need for immunosuppression. Published data regarding HSCT and LT is limited to case reports. In an 18-year-old male with hyper-IgE syndrome resulting in primary immunodeficiency, HSCT was performed 5 weeks after LT, leading to improvement of the underlying disease as well as hepatic manifestations.[106] Despite infectious complications and poor prognosis, sequential HSCT and LT may be considered as a therapeutic option for selected patients with CVID. However, more data is required to confirm the viability of this approach and to identify those who could derive clinical benefit.

Future directions

Anticoagulants and statins

As discussed above, NRH is thought to be caused by impaired blood flow to hepatocytes due to potential vascular damage and is thus described as PSVD. Given the association of PSVD with prothrombotic states,[43–45] the therapeutic role of anticoagulants is of particular interest. However, outside CVID, in patients with PSVD, anticoagulants including low molecular weight heparin, vitamin K antagonists and direct oral anticoagulants are only recommended for the treatment of patients with prothrombotic states or manifest portal vein thrombosis.[72,107] The Baveno VII consensus document does not address the use of anticoagulants to target the underlying disease biology or for the treatment of CVID-associated NCPH.[72] As there is limited data on the potential benefits of anticoagulation on progression of NRH,[108] a potential effect on the underlying pathology should be subject to further investigation in CVID (Fig. 3). This includes assessing the optimal duration of prophylactic/therapeutic anticoagulants in the course of disease.

Furthermore, it has been demonstrated that statins, particularly simvastatin, result in a significant decrease in HVPG,[109,110] as well as improved survival after variceal bleeding in patients with cirrhotic portal hypertension.[111] The observed effects suggest simvastatin as a potential therapeutic option for CVID-associated NRH progression and manifest NCPH (Fig. 3), although clinical trials are needed to validate this hypothesis.

Targeting the gut-liver axis

Given the association of NRH and enteropathy with microbial translocation, CVID-associated impairment of the intestinal endothelial barrier should be examined. The gut-liver axis is involved in a variety of liver diseases[112] and could open up new therapeutic options involving the microbiome. One study[62] observed reduced *Bifidobacterium* in CVID gut microbiota. The presence of *Bifidobacteria* was associated with improved gastrointestinal barrier and decreased plasma LPS levels in healthy control patients, thus pointing towards a potential benefit of probiotics containing *Bifidobacterium*.[113] Poto *et al.*[114] suggest the administration of *A. muciniphila* as a live microorganism to preserve epithelial function and thus prevent microbial translocation. Furthermore, dysbiosis is an adverse effect of antibiotics,[115] which are widely used in CVID management. However, data on long-term antibiotic treatment and gut microbiota alterations in patients with CVID are lacking. Rifaximin, which has been shown to decrease LPS levels in cirrhosis,[116–118] did not have any effect on plasma LPS in patients with CVID.[118] Faecal microbiota transplantation (FMT) increases microbial diversity (reduced in CVID[62]) in several conditions[119,120] but has not been studied yet in PID. Reports of pathogen transmission via FMT[121] emphasize the need for enhanced donor screening and faecal specimen preparation for immunocompromised patients, including those with CVID.[114]

Summary and conclusions

Clinical management of CVID-related liver disease includes screening, diagnostic work-up and treatment. Clinical care requires a multi-disciplinary approach involving experts specialized in vascular liver diseases and CVID. The initial work-up should include LFTs as well as abdominal ultrasound and TE. A liver biopsy is highly recommended when evidence of liver disease is present in the initial work-up to investigate the nature of liver disease and rule out other causes. Early diagnosis is essential to slow progression of disease and decrease mortality.

Treatment approaches targeting the underlying disease biology include immunosuppressants which might be beneficial for patients with CVID displaying AIH/AIH-like disease. Since some immunosuppressants (such as high-dose thiopurines) are associated with the occurrence of NRH and have been shown to contribute to poor outcomes through aggravation of the underlying immunodeficiency, they should be used with caution and under close surveillance. Based on the scarcity of CVID-specific data, we recommend prophylactic management of portal hypertension according to guidelines for cirrhotic PH. In patients with CVID and advanced liver disease, standard interventions for portal hypertension, such as TIPS, improve NCPH significantly but are unfortunately associated with a high rate of infectious complications and consequently poor prognosis.[93] Selected patients may benefit from LT. A careful benefit-risk evaluation will help guide decision making. Specific guidelines for LT will need to be established.

The overall unsatisfactory management and lack of data warrants additional research. Future approaches of interest include

anticoagulants and statins, which might delay NRH progression due to its underlying microvascular pathology, or FMT to improve the underlying pathology of the gut-liver axis in CVID.

Collectively, the still unsatisfactory treatment options highlight the need for a better understanding of disease biology to develop improved therapeutic approaches. In particular, interventions directed at the mechanistic events leading to liver disease progression are needed to improve patient prognosis.

Finally, specific advances in therapies targeting the underlying CVID (*e.g.* correcting genetic perturbations) without the requirement for lifelong immunosuppression will help to address the hepatic manifestations of CVID.

Methods

Criteria and resources for literature research

A literature search was performed using PubMed and Google Scholar databases from May 1990 until June 2023 with the following key words: "CVID", "liver disease", "NRH", "NCPH", "portal hypertension", "PSVD", "gut-liver axis", "microbiome", "TIPS", "immunosuppressants", "diagnosis", "therapy", "liver transplantation", "HSCT", "anticoagulants", "statins", "LFTs", "imaging", "ultrasound", and "transient elastography". References in this narrative review included articles describing liver disease in patients with CVID, as well as articles relating to NRH and/or PSVD and/or NCPH in patients without CVID, as indicated in the text.

Abbreviations

AIH, autoimmune hepatitis; AZA, azathioprine; CVID, common variable immunodeficiency; EVL, endoscopic variceal ligation; FMT, faecal microbiota transplantation; HVPG, hepatic venous pressure gradient; HSCT, haematopoietic stem cell transplantation; LFT, liver function tests; LPS, lipopolysaccharide; LSM, liver stiffness measurement; LT, liver transplantation; NCPH, non-cirrhotic portal hypertension; NRH, nodular regenerative hyperplasia; NSBBs, non-selective beta-blockers; PID, primary immunodeficiency; PSVD, porto-sinusoidal vascular disease; SSM, spleen stiffness measurement; TE, transient elastography; TIPS, transjugular intrahepatic portosystemic shunt.

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Conflict of interest

The authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

RTC conceptualized the review, LSB and RTC wrote the review. LSB assembled the figures. AS provided histopathology analyses shown in Fig. 1 and edited the manuscript.

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Supplementary data

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Author names in bold designate shared co-first authorship

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