

Liver disease is common in patients with common variable immunodeficiency and predicts mortality in the presence of cirrhosis or portal hypertension



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Clinical Implications

- Liver disease is common in patients with common variable immunodeficiency, and monitoring (eg, annual liver function tests and ultrasound imaging) is important for early detection of liver disease. Importantly, referral to hepatology services is advised if liver disease is suspected as the presence of cirrhosis or portal hypertension portends a poor prognosis.

TO THE EDITOR:

Common variable immunodeficiency (CVID) is characterized by impaired B-cell function with hypogammaglobulinemia, without profound T-cell dysfunction. CVID affects 1 of 25,000 to 50,000 of the population with equal sex preponderance. CVID affects multiple organ systems and is associated with recurrent infections, autoimmunity, granulomas, and malignancy¹ (summarized in Table I). Abnormal liver function tests (LFTs) are associated with worse outcomes in CVID,² but there is limited knowledge about which liver-related factors affect outcome; hence, we present the largest characterization of liver pathology in CVID, detailing aspects of liver disease associated with mortality.

We evaluated the management and outcomes of the CVID cohort at our center for clinical reasons and service evaluation; ethical clearance for this retrospective anonymized study was not required according to UK law. We analyzed age, sex, time, and mode of presentation to services, flow cytometry data, organ system involvement, liver blood parameters and imaging, analysis of liver histology, involvement of hepatology services, and mortality. Data were analyzed in GraphPad Prism. Eighty-six patients met assessment criteria as detailed in the CONSORT diagram (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

We found a much higher prevalence of liver disease (79%, n = 68/86) than previously reported.³ The high incidence noted here is probably reflective of the fact that our study is based on patients with in-depth liver profiling (at least one of abnormal LFT profile, abnormal liver imaging, or abnormal liver histology) and requirement of active follow-up for inclusion. Our study found that patients with CVID without liver disease had normal liver

biochemistry and imaging. However, patients with liver disease had statistically significant elevations in LFTs and thrombocytopenia (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). Thrombocytopenia occurred in 32% of patients with liver disease compared with 11% of those without; this is in keeping with the higher incidence of splenomegaly in those with liver disease (54% vs 22% in those without liver disease). Abnormal liver imaging was present in 77% of those with liver disease, the majority of which was described as heterogeneous echotexture, consistent with the commonest histologic abnormality of nodular regenerative hyperplasia (NRH) with either coexisting inflammation or coexisting granulomatous disease (Table I). We have previously referred to the presence of NRH-like changes and lobular/interface hepatitis as intrinsic CVID-related liver disease, which can be associated with both cirrhosis and portal hypertension (PHTN).⁴

NRH is notoriously difficult to diagnose even by experienced liver pathologists⁵ so a high index of suspicion is required to look for it, as was performed in this study. Our study is the largest histologic liver series in CVID and shows a high incidence of NRH in CVID (32%, n = 28/86), consistent with another smaller but detailed study³ and both substantially higher than larger studies that outline liver pathology without detail (5% to 20%).^{6,7} Six patients had noncirrhotic PHTN, which is classically associated with NRH,⁸ whereas 9 patients had histologic cirrhosis with NRH-like changes, countering assertions of the 2 diagnoses being mutually exclusive.^{6,7}

We found stark differences in mortality between those with liver disease and those without: crude death rates were 19 of 68 (28%) and 1 of 18 (6%), respectively. Kaplan-Meier analyses show that those with liver disease have statistically worse survival, especially after age 35 years (Figure 1, A). The hazard ratio of having liver disease is 3.5 (95% confidence interval, 1.2-9.9; $P = .0195$), higher than previous reports.² Time from CVID diagnosis to death in those with liver disease was 8 years (for median; 11 years for mean). When patients with liver disease are subclassified, those with cirrhosis and/or PHTN fare much worse than those without (Figure 1, B; hazard ratio, 4.2; 95% confidence interval, 1.5-11.9; $P = .0005$), even when we correct for 4 patients who were liver-transplanted. Liver disease confers age-standardized mortality ratios of 25.9 in those with CVID compared with 8.8 in the general population.⁹

We noted that in a subgroup of 5 patients with abnormal LFTs and normal appearance of their liver who were liver-biopsied on the basis of splenomegaly, the histology was consistent with NRH. A further 13 patients with abnormal LFT and normal appearing liver have not been biopsied, but may have (had) significant liver disease as their survival curves parallel that of liver disease (not shown). This suggests that patients with persistently abnormal LFTs should have a liver biopsy if it is safe to proceed as this may allow us to prognosticate about their outcome. NRH portends a poorer prognosis likely because it often occurs with cirrhosis or PHTN, but the prognosis is worse if it coexists with both cirrhosis and PHTN (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org). NRH is notoriously difficult to diagnose even by experienced liver pathologists⁵ so a high index of suspicion is required to look for it, as was performed in this study.

TABLE I. Baseline characteristics of CVID patients with or without liver disease

Characteristics	CVID without liver disease n = 18 (21%)	CVID with liver disease n = 68 (79%)	P value
Male, n (%)	6 (33%)	39 (57%)	.11 (ns)
Mean age of alive patients (y)	48.1	47.7	
Mean age of death (y)	83	61	
Crude mortality ratio	1 of 18 (6%)	19 of 68 (28%)	
Recurrent respiratory tract infections, n (%)	15 (83%)	54 (79%)	1.00 (ns)
Autoimmunity, n (%)	2 (11%)	9 (13%)	1.00 (ns)
Granulomas, n (%)	1 (6%)	13 (19%)	.28 (ns)
Malignancy, n (%)	2 (11%)	17 (25%)	.34 (ns)
Gastrointestinal manifestations, n (%)	3 (17%)	24 (35%)	.16 (ns)
Splenomegaly, n (%)	4 (22%)	37 (54%)	.011
Liver biochemical tests pattern			
Alkaline phosphatase (ALP)	D = 18 (100%)	A = 5 (7.4%) B = 26 (38.2%) C = 16 (23.5%) D = 21 (30.9%)	
Alanine transaminase (ALT)	D = 18 (100%)	A = 3 (4.4%) B = 13 (19.1%) C = 25 (36.8%) D = 27 (39.7%)	
Bilirubin	D = 18 (100%)	A = 1 (1.5%) B = 8 (11.8%) C = 5 (7.4%) D = 54 (79.4%)	
Imaging			
US Liver Doppler	Normal liver = 18 (100%)	Heterogeneous = 26 (38%) Normal liver = 16 (24%) Fatty liver = 13 (19%) Cirrhotic = 5 (7%) Hepatomegaly = 4 (5.9%)	
Histology	Not performed = 18 (100%)	Performed = 34 (50%) NRH = 28 (41%) NRH + inflammation = 18 (53%) NRH + granuloma = 10 (29%) NASH = 5 (15%) Nonspecific inflammation = 1 (3%)	
Liver disease complications			
Cirrhosis, n (%)		12 (18%)	
Portal hypertension, n (%)		14 (21%)	

CVID, Common variable immunodeficiency; NASH, nonalcoholic steatohepatitis; NRH, nodular regenerative hyperplasia; ns, not significant.

Liver biochemical test pattern: A, progressive elevation; B, persistently abnormal or variable; C, variable to normal; D, normal.

Although this study does not address the clinical significance of NRH, we do note that the NRH-like disease process recurred in 75% of a cohort of patients with CVID receiving an orthotopic liver transplant, leading to cirrhosis and death.⁴

To date, this is the most detailed study of liver disease in CVID, which classically manifests with histologic NRH. The additional presence of cirrhosis and/or PHTN confers a very poor prognosis, especially when age is greater than 35 years. Therefore, we recommend that patients with CVID who have normal LFTs and are over 30, or have persistently abnormal LFTs, should have annual monitoring of their LFTs, clotting profile, and annual abdominal imaging to look for evidence of abnormal liver appearance, splenomegaly, and other features of PHTN. Abnormalities should be promptly referred to a

hepatologist for workup, which should include transient elastography and/or liver biopsy. If PHTN is evident, management for ascites, hepatic encephalopathy, and upper gastrointestinal varices should be instigated to reduce morbidity and mortality.

In CVID patients with cirrhosis, liver transplantation remains theoretically the only effective treatment, although in practice outcomes have been poor due to disease recurrence.⁴ Hematopoietic stem cell transplantation (HSCT) alongside liver transplantation could be considered as an option for CVID patients with liver disease as there is benefit seen in other primary immunodeficiencies.¹⁰ However, HSCT in CVID is associated with significant complications such as severe infections and graft versus host disease; with a mortality of 48%, it is not a feasible treatment

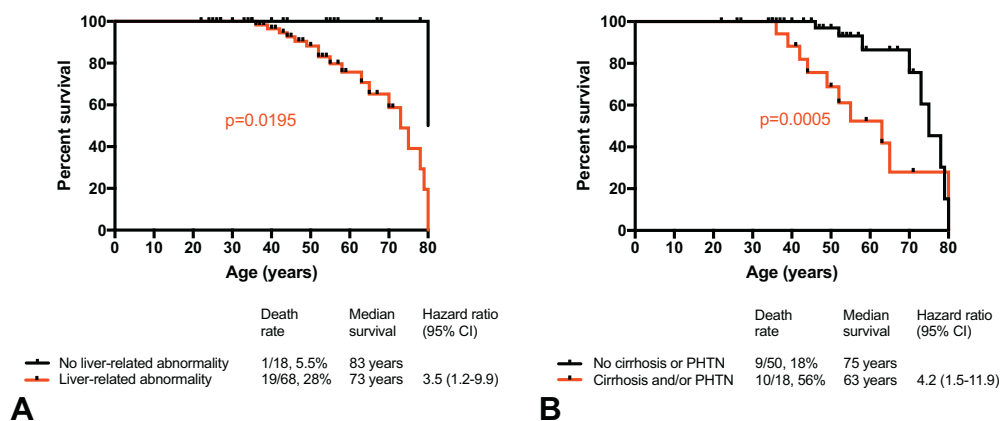


FIGURE 1. Survival curves in common variable immunodeficiency patients (A) with/without liver disease and (B) with/without cirrhosis and/or portal hypertension (PHTN). *CI*, Confidence interval.

option for adults at present.^{11,12} There is an urgent need for further basic science, clinical research, and therapeutic development for patients with CVID, especially those with liver involvement.

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VA, DSK, and WJHG initiated the investigation of liver disease in patients with CVID. VA and MF designed the study and analyzed the data. VA, MF, LK, NM, and MQ collated the data. AD, RB, and SD performed histologic reviews. VA wrote the manuscript. All authors made intellectual contributions and modifications to the manuscript.

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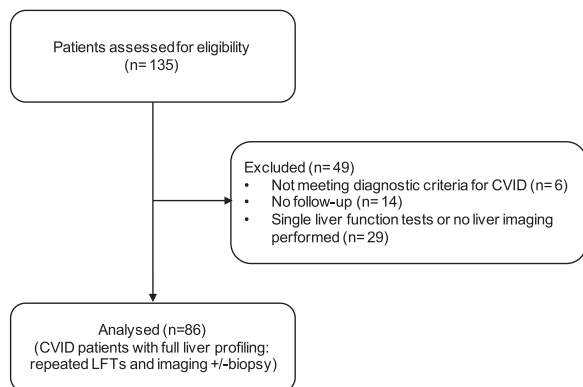


FIGURE E1. Consort diagram showing patient selection for inclusion in this study. European Society of Immunodeficiencies diagnostic criteria were used for CVID. *CVID*, Common variable immunodeficiency; *LFT*, liver function test.

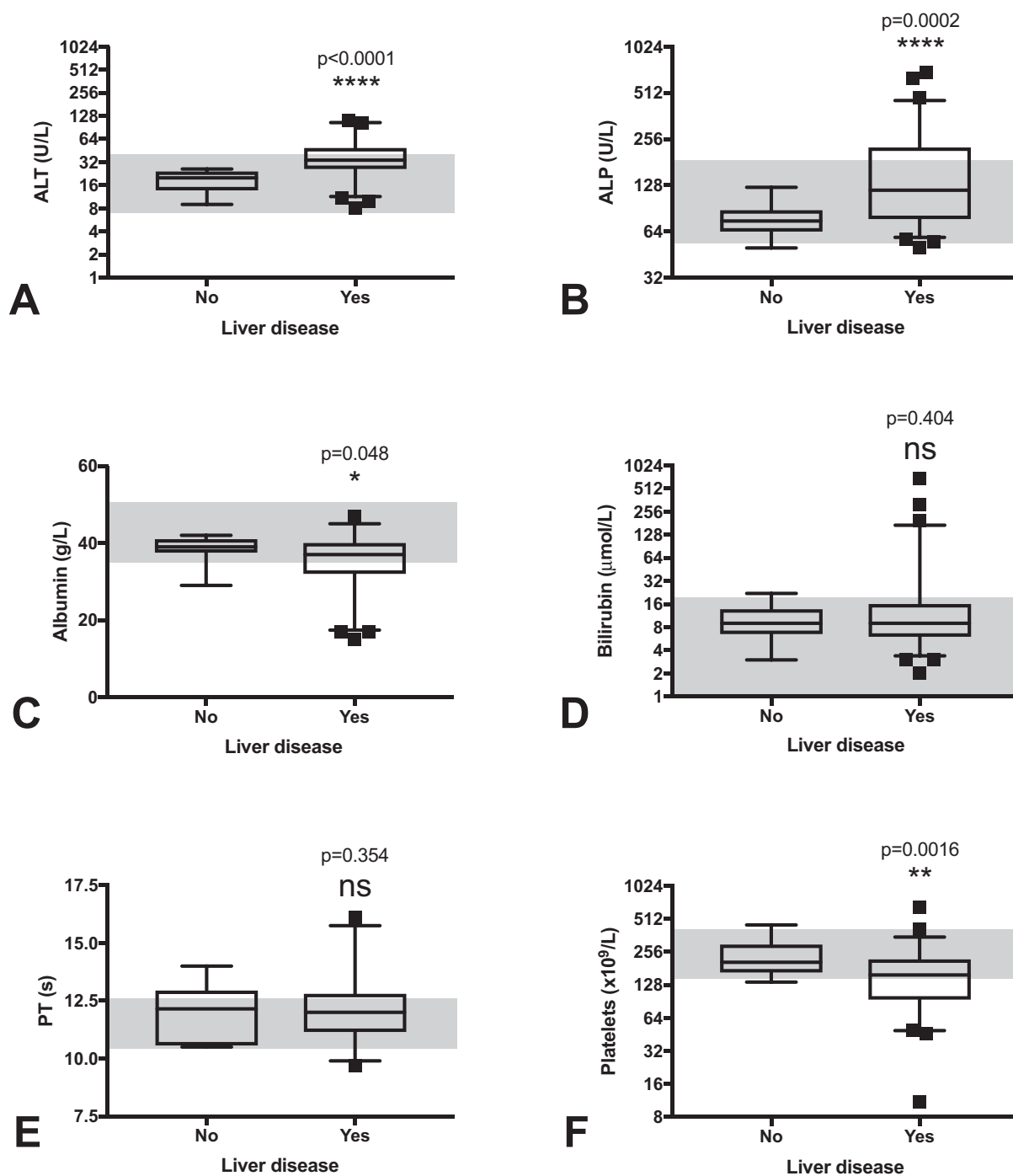


FIGURE E2. Liver function tests in those with and without liver disease. **A**, alkaline transaminase (ALT); **B**, alkaline phosphatase (ALP); **C**, albumin; **D**, bilirubin; **E**, prothrombin time (PT); and **F**, platelet count. Boxes indicated median and interquartile ranges with bars showing 5-95 percentiles. Statistical significance is indicated by *P* value.

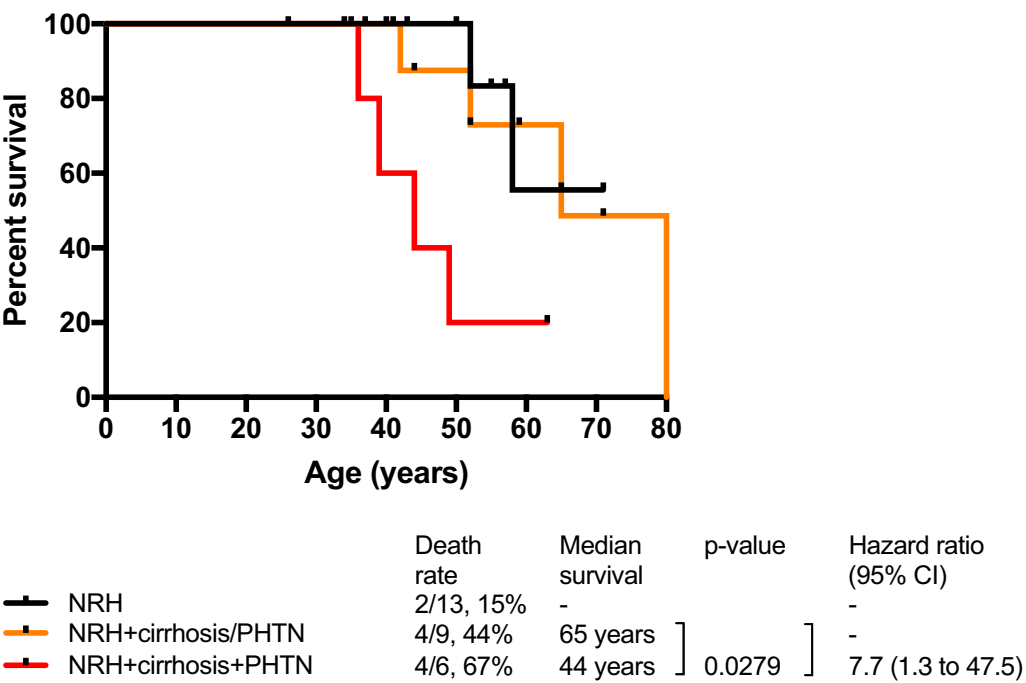


FIGURE E3. Survival curves in patients with NRH only, NRH plus cirrhosis or PHTN, and NRH with cirrhosis and PHTN. *NRH*, Nodular regenerative hyperplasia; *PHTN*, portal hypertension.

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