Received: 21 November 2023 | First decision: 20 December 2023 | Accepted: 11 May 2024

DOI: 10.1111/apt.18060

AP&T Alimentary Pharmacology & Therapeutics WILEY

Portal hypertension and its prognostic implications in patients with Wilson's disease

Lukas Burghart[1,2,3,4,5] | Peter Ferenci[1,†] | Oleksandr Petrenko[1,2,3,6,7,8] | Mattias Mandorfer[1,2,3] | Michael Schwarz[1,2] | Michael Gschwantler[4,5] | Michael Trauner[1,3] | Thomas Reiberger[1,2,3,6,7,8] | Albert Friedrich Stättermayer[1,2,3]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

[2]Vienna Hepatic Hemodynamic Laboratory, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

[3]Rare Liver Disease (RALID) Center of the European Reference Network for Rare Hepatological Diseases (ERN RARE-LIVER), Medical University Vienna, Vienna, Austria

[4]Department of Internal Medicine IV, Wilhelminenspital, Vienna, Austria

[5]Sigmund Freud University, Vienna, Austria

[6]Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD), Vienna, Austria

[7]CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

[8]Christian-Doppler Laboratory for Portal Hypertension and Liver Fibrosis, Medical University of Vienna, Vienna, Austria

Correspondence
Thomas Reiberger, Division of Gastroenterology and Hepatology, Department of Medicine III, Waehringer Guertel 18-20, Vienna A-1090, Austria.
Email: thomas.reiberger@meduniwien.ac.at

Summary

Background and Aims: Wilson's disease may progress to cirrhosis and clinically significant portal hypertension (CSPH). We aimed to assess the prevalence and prognostic impact of CSPH-related features on hepatic decompensation and transplant-free survival in patients with Wilson's disease.

Methods and Results: About 137 patients with Wilson's disease (Leipzig score ≥4), followed for a median observation period of 9.0 (3.9–17.7) years at the Vienna General Hospital, were included in this retrospective study. Overall, 49 (35.8%) developed features of CSPH: 14 (10.2%) varices, 40 (29.2%) splenomegaly, 20 (14.6%) ascites, 18 (13.1%) hepatic encephalopathy and 3 (2.2%) experienced acute variceal bleeding. Overall, 8 (5.8%) patients died, including three deaths caused by CSPH-related complications. Within 10 years, compensated patients with features of CSPH developed more decompensation events (8.3% vs. 1.5% in patients without CSPH, $p = 0.3$) and had worse transplant-free-survival (91.7% vs. 98.6%), which further declined in patients with hepatic decompensation (26.7%, log-rank: $p < 0.0001$). Patients with liver stiffness <15 kPa and normal platelets (≥150 G/L) were less likely to decompensate within 10 years (2.6% vs. 8.4%, $p = 0.002$) and had a better 10-year transplant-free-survival (97.7% vs. 83.9%, $p = 0.006$).

Conclusions: Patients with Wilson's disease developing features of CSPH are at an increased risk for hepatic decompensation and liver-related mortality, warranting for regular screening and timely initiation of effective CSPH-directed treatments.

†Deceased author.

The Handling Editor for this article was Professor Gideon Hirschfield, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Wilson's disease (WD) is a rare, autosomal-recessive disorder characterised by impaired hepatic copper transport with subsequent copper accumulation in the liver, the central nervous system and other tissues.[1,2] The causative genetic defect was found within the *ATP7B* gene on chromosome 13, encoding for a copper-transporting P-type ATPase. *ATP7B* resides in the trans-Golgi network of hepatocytes and is responsible for copper transport into secretory pathways and incorporation into apo-ceruloplasmin.[3,4]

Disease manifestation can vary widely: patients most commonly present with liver disease, neuropsychiatric symptoms and ophthalmologic findings, for example Kayser–Fleischer corneal rings.[5] Hepatic disease ranges from clinically asymptomatic cases with only mild elevation of liver enzymes and hepatic steatosis to clinically overt advanced chronic liver disease (ACLD) with features of clinically significant portal hypertension (CSPH; i.e. varices, splanchnic collaterals, splenomegaly) or even symptoms of hepatic decompensation (seen as variceal haemorrhage, ascites or hepatic encephalopathy). In rare cases, patients present with fulminant hepatic failure (mostly based on preexisting ACLD) with Coombs' negative haemolytic anaemia.

Chronic liver injury, independent of its aetiology, induces fibrogenesis, ultimately leading to cirrhosis.[6] Remodelling of intrahepatic vasculature increases intrahepatic vascular resistance, which is, together with the vast abundance of vasoconstrictive agents, mainly responsible for the development of portal hypertension.[7] Portal hypertension itself is the main driver for decompensating events and impaired transplant-free survival (TFS)[6] which explains the generally applied treatment approach, to lower portal hypertension using non-selective beta-blockers (NSBBs)[8] and justifies the necessity to screen for portal hypertension regularly.[9]

In a previously published study by Ferenci et al.,[10] the proportion of WD patients with histologically proven cirrhosis increased from 7% (at age of 6 years) to 49% until the age of 16, whereas the prevalence of cirrhosis was found to be 50%–60% in adults. In WD patients without cirrhosis, steatosis is the most common histological finding.[11] Nonetheless, patients receiving adequate chelator treatment (d-penicillamine, triethylenetetramine) have a good long-term prognosis. In a previous study with a mean follow-up time of 14.8 years the majority of WD patients either remained symptom-free, clinically stable or even improved under chelator treatment. However, up to 25% deteriorated, underwent liver transplantation (LTX) or died under therapy, with the presence of cirrhosis appearing to be the strongest predictor of (LTX) and death.[12] In other previously published studies the rate of liver-related death or LTX ranged from 2.1% to 21.1% within a mean follow-up duration of 16.7 years.[5,13–17]

Despite the abundance of studies on WD and ACLD, which mainly focus on the prevalence of histologically proven cirrhosis,[10,15,18,19] only little insight has been given into the prevalence and the prognostic impact of CSPH-related features so far.[20] Therefore, this single-centre retrospective study aims to evaluate the prevalence of clinical features of CSPH in WD and their impact on subsequent hepatic decompensation, requirement of LTX, TFS and overall mortality.

2 | PATIENTS AND METHODS

2.1 | Study population

Patients with WD who were managed between Q1/2005 and Q4/2021 at the Vienna General Hospital were identified from preexisting databases (Ferenci et al.[21]). WD was defined and confirmed by Leipzig Score ≥ 4[22] based on laboratory (serum ceruloplasmin, urinary copper excretion, hepatic copper content) and clinical criteria (presence of neuropsychiatric symptoms, Kayser-Fleischer corneal rings, Coombs' negative haemolysis) as well as genetic testing.[1] Patients with features of organ involvement (e.g. neuropsychiatric symptoms, elevation of serum transaminases) received induction therapy with d-penicillamine, which was switched to trientine in case d-penicillamine was not well tolerated. Patients with asymptomatic Wilson's disease and absence of organ involvement as well as patients on maintenance therapy received d-penicillamine, trientine or zinc, which is in accordance to current guidelines (Figure 1).[23]

2.2 | Study parameters

Demographic, biochemical and clinical data were extracted from individual patient records at the time of WD diagnosis and throughout follow-up. Routine blood sampling every 6 months allowed for platelet quantification on a regular basis. Reports on imaging studies, such as CT, MRI and ultrasound (the latter was performed on a yearly basis in patients without ACLD as well as on a 6-month basis in patients with evidence of ACLD[6]) were searched for portosystemic collaterals, portal vein thrombosis and presence of splenomegaly.[24] Information regarding presence of gastroesophageal varices and endoscopic interventions on varices were obtained from endoscopy reports. Results of liver stiffness measurements (LSM) were recorded if available. As of now, we evaluate liver stiffness via transient elastography in patients with Wilson's disease on a yearly basis, but this has not been the case during the earlier years of our cohort build-up.

2.3 | Definition of CSPH and compensated versus decompensated ACLD

CSPH was defined by the presence of at least one of the following criteria[25,26]: (i) gastroesophageal varices, (ii) splenomegaly (longitudinal diameter [LDM] >11 cm),[24] (iii) portosystemic collaterals; (iv) ascites (excluding non-hepatic causes), (v) variceal bleeding, (vi) hepatic encephalopathy or (vii) thrombocytopenia (platelets <150 G/L).

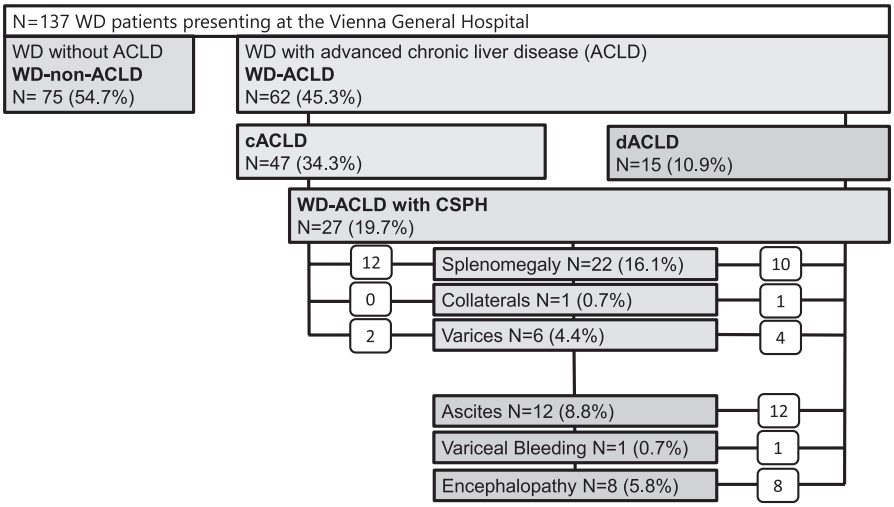

FIGURE 1 Presence of ACLD and clinical features of CSPH at baseline.

ACLD was defined by at least one of the following criteria: (i) liver histology showing F3/F4 fibrosis, (ii) LSM ≥10 kPa, or (iii) presence of CSPH-related features (as described above). Patients with compensated advanced chronic liver disease (cACLD) were characterised by at least one feature of ACLD and the absence of any previous or current decompensating events.[27–29] Patients with decompensated ACLD (dACLD) presented at least one of the following characteristics: ascites, variceal bleeding, overt hepatic encephalopathy or death related to CSPH.[27–29] LSM were obtained using transient elastography (FibroScan®, Echosens) when clinically indicated, as previously described.[30,31] Presence and size of gastroesophageal varices was recorded according to Austrian Billroth III guidelines.[32]

According to the BAVENO VII recommendations[26] we divided our population into the following groups: (i) patients without ACLD (non-ACLD), (ii) patients with compensated ACLD (cACLD) but without features of CSPH, (iii) patients with cACLD and features of CSPH, (iv) patients with dACLD. For further analysis, patients were identified with one of the above-mentioned ACLD stages based on their clinical presentation at baseline, which was defined as time of WD diagnosis.

Calculation of the cumulative incidence of decompensation, requirement of LTX, TFS and overall mortality for clinical features of CSPH (as outlined above) was based on the period between WD diagnosis and decompensation or death/LTX.

This study was conducted in accordance with both the Declarations of Helsinki (1964) and Istanbul (2008). Due to the retrospective nature of this study, informed consent of the patients included is not provided, which was approved by the Ethics committee of the Medical University of Vienna (EK 2464/2020).

2.4 | Statistical analysis

Statistical analysis was performed using IBM SPSS 28. Kolmogorov–Smirnov test was applied to distinguish between variables in Gaussian and non-Gaussian distribution. Mean and standard deviation (SD) as well as median and interquartile range (IQR) were used wherever applicable. Graph-pad Prism 9 was utilised to compute Kaplan–Meier plots to illustrate cumulative incidence of decompensation, requirement of LTX, TFS and overall mortality.

Cumulative incidence of decompensation, TFS, requirement of LTX and overall mortality were calculated based on the elapsed time between WD diagnosis and the respective outcome. Differences between time-dependent event rates (decompensation, TFS) were tested by log-rank test. Cox regression analysis was used to evaluate the impact of potential risk factors on decompensation, LTX or death.

3 | RESULTS

3.1 | Baseline patient characteristics

The study population included 137 patients with Wilson's disease (median age: 41.5 years [IQR: 31.2–56.3], f/m: 68/69, median MELD-Score: 8 [IQR: 7–10]; Table 1, Figure 1). Most patients received d-penicillamine (70.1%), a fifth was treated with trientine (21.2%) and six (4.4%) patients received zinc monotherapy. Another six (4.4%) patients were left without pharmacotherapy as they were referred to LTX due to decompensated liver disease at the time of diagnosis. Of note, we did not observe significant differences between the above-mentioned WD-specific pharmacotherapeutic approaches regarding the occurrence of decompensated liver disease, LTX or death (FFI; Figure S1, Tables S4 and S5).

At baseline, 35 (25.5%) patients had cACLD without CSPH, 12 patients (8.8%) were diagnosed with cACLD with CSPH, whereas another 15 (10.9%) patients had already progressed to dACLD.

In a sub-analysis of patients with CSPH at baseline ($n=12$ cACLD with CSPH and $n=15$ dACLD) we observed that $n=3$ patients with cACLD and CSPH at baseline improved to cACLD without CSPH during follow-up, while receiving d-penicillamine, whereas $n=3$ patients with dACLD at baseline, receiving d-penicillamine ($n=2$) and trientine ($n=1$), achieved hepatic recompensation[26] during follow-up (FFI; Figure S2).

Overall, throughout a median follow-up of 9.0 (IQR: 3.9–17.7) years, 74 (54.0%) patients presented features suggestive of ACLD.

TABLE 1 Patient characteristics.

Patients	N = 137 (100%)
Age at diagnosis, median, IQR	41.5 (31.2–56.3)
Sex (Women/Men, *N*, %)	68/69 (49.6/50.4)
Liver biopsy, *N* (%)	88 (64.2)
Fibrosis on liver biopsy, *n* (%), *n* = 88	F0: 11 (12.5) F1: 13 (14.8) F2: 16 (18.2) F3: 10 (11.4) F4: 38 (43.2)
Aspartate aminotransferase (IU/L, mean ± SD)	50.4 (±56.2)
Alanine aminotransferase (IU/L, mean ± SD)	66.5 (±92.9)
Neuropsychiatric symptoms (*n*, %)	39 (28.5)
Hepatic presentation[a] (*n*, %)	125 (91.2)
Fulminant hepatic failure at diagnosis, *N* (%), *n* = 81	3/140 (2.1)[b]
Neuropsychiatric symptoms and liver disease, *N* (%)	35 (25.5)
Coombs-negative haemolytic anaemia, *N* (%)	13 (9.5)
Ceruloplasmin (IQR) mg/dL	10 (9–14.9)
Kayser-Fleischer corneal ring, *N* (%)	41 (29.9)
Liver copper, µg/g (IQR), *n* = 81	700 (341.5–1047)
ATP7B variant analysis	103 (75.2%) variants on both alleles identified 30 (21.9%) variants on one allele identified 4 (2.9%) no variant identified
MELD-Score, median (IQR)	8 (7–10)
LSM (IQR), *n* = 68	7.7 (5.4–13.5) kPa
Treatment with d-penicillamine, *N* (%)	96 (70.1)
Treatment with trientine, *N* (%)	29 (21.2)
Treatment with zinc monotherapy, *N* (%)	6 (4.4)
Non-adherence to treatment, *N* (%)	15/131 (11.5)

ACLD-status	At baseline	Overall
Non-ACLD, *N* (%)	75 (54.7)	63 (46.0)
cACLD, *n* (%)	47 (34.3)	49 (35.8)
cACLD without CSPH, *N* (%)	35 (25.5)	25 (18.2)
cACLD with CSPH, *N* (%)	12 (8.8)	24 (17.5)
dACLD (all with CSPH), *N* (%)	15 (10.9)	25 (18.2)
Features of CSPH, *N* (%)	27/137 (19.7%)	49/137 (35.8%)
Splenomegaly	22/137 (16.1%)	40/137 (29.2%)
Portosystemic collaterals	1/137 (0.7%)	4/137 (2.9%)
Gastroesophageal varices	6/137 (4.4%)	14/137 (10.2%)
Ascites	12/137 (8.8%)	20/137 (14.6%)
Variceal bleeding	1/137 (0.7%)	3/137 (2.2%)
Hepatic encephalopathy	8/137 (5.8%)	18/137 (13.1%)
Time between WD diagnosis and CSPH (years, mean ± SD)	3.9 ± 7.5	

TABLE 1 (Continued)

CSPH-treatment and outcomes	
Median follow-up (years, median, IQR)	9.0 (3.9–17.7)
NSBB therapy, *N* (%)	12/137 (8.8)
NSBB prescription in CSPH patients, *N* (%)	10/49 (20.4)
NSBB prescription in dACLD patients, *N* (%)	7/25 (28.0)
EBL therapy, *N* (%)	8/49 (16.3)
TIPS, *N* (%)	1/49 (2.0)
LTX, *N* (%)	16/137 (11.7)
All-cause death, *N* (%)	8/137 (5.8)
Liver-related death, *N* (%)	6/137 (4.4)
CSPH-related death, *N* (%)	3/137 (2.2)

Abbreviations: ACLD, advanced chronic liver disease; cACLD, compensated ACLD; CSPH, clinically significant portal hypertension; dACLD, decompensated ACLD; EBL, endoscopic band ligation; IQR, Interquartile range; LSM, Liver stiffness measurement; LTX, liver transplantation; MELD, Model End Stage Liver Disease Score; NSBB, non-selective beta-blocker; SD, standard deviation; TIPS, transjugular intrahepatic portosystemic shunt.

[a]Clinical and laboratory signs of liver disease at the time of WD diagnosis.

[b]These patients were excluded from further analysis.

Forty-nine patients (35.8%) developed features of CSPH, with 24 (49.0%) patients remaining compensated, whereas 25 (51.0%) patients progressed to dACLD.

Splenomegaly (median LDM = 14.7 cm IQR: 12.5–17.0 cm) was the most frequent CSPH-related feature, affecting 40 (29.2%) patients, oesophageal varices were found in 14 (10.2%) and portosystemic collaterals in 4 (2.9%) patients, respectively. Of note, only 20.4% (*n* = 10) of all patients with clinical signs of CSPH received treatment with NSBBs. Twenty (14.6%) patients developed ascites, whereas acute variceal bleeding and hepatic encephalopathy occurred in three (2.2%) and 18 (13.1%) patients, respectively.

3.2 | Incidence of decompensation

Patients without ACLD at baseline showed a 1.5% 5Y decompensation rate, whereas patients with cACLD but without CSPH and cACLD with CSPH had a numerical increase in their 5Y decompensation rates to 2.9% and 8.3% (log-rank: $p = 0.3$), respectively (Tables 1 and 2; Figure 2).

Presence of oesophageal varices was associated with a 5Y decompensation rate of 11.1% whereas compensated patients with splenomegaly revealed a numerically lower 5Y decompensation rate of 3.4%; however, statistical significance was not proven (log-rank: $p = 0.27$).

3.3 | Liver TFS

During follow-up 16 (11.7%) patients were referred to receive LTX and eight (5.8%) patients eventually died (2 patients received LTX

TABLE 2 Incidence of decompensation according to clinical characteristics of patients with WD.

Variable	Cumulative incidence of decompensation			
	1–3 years	5 years	10 years	*N* total[a]
Overall decompensation rate[b]	2.6%	2.6%	3.8%	10 (8.2%)
Normal PLT and LSM <15 kPa	2.6%	2.6%	2.6%	3 (3.7%)
Thrombocytopenia (<150 G/L) or LSM ≥ 15 kPa	4%	4%	8.4%	7 (26.9%)
No ACLD	1.5%	1.5%	1.5%	3 (4%)
cACLD without CSPH	2.9%	2.9%	6.2%	6 (17.1%)
cACLD with CSPH	8.3%	8.3%	8.3%	1 (8.3%)
F0–F3	0.0%	0.0%	0.0%	1 (2.5%)
F4	12%	12%	16.4%	8 (30.8%)
Splenomegaly	3.4%	3.4%	7.8%	7 (24.1%)
Oesophageal varices	11.1%	11.1%	25.9%	3 (33.3%)

Note: Risk of hepatic decompensation according to distinct clinical characteristics within 1–3 years, 5 years and 10 years of follow-up.

Abbreviations: ACLD, advanced chronic liver disease; cACLD, compensated ACLD; dACLD, decompensated ACLD; CSPH, clinically significant portal hypertension; LSM, Liver stiffness measurement; PLT, platelets.

[a]Number of patients with at least one decompensating event (%) throughout the entire follow-up period.

[b]Patients with decompensated liver disease at baseline (time of WD diagnosis; $n=15$) were excluded, leaving $n=122$ within this analysis.

before death and were, therefore, censored at the time of LTX during the following analysis of TFS, leaving a total of $n=22$ events), including three deaths that were attributed to CSPH-related complications (ACLF $n=1$, SBP $n=1$ and fatal variceal bleeding $n=1$; Tables 1 and 3, Figure 3, Figure S3).

10Y TFS of the entire cohort was 88.3%. WD patients without ACLD and patients with cACLD but without CSPH had significantly higher 1-, 5- and 10-Y TFS rates compared to WD patients with cACLD and CSPH (log rank: $p=0.02$) and patients with dACLD (log-rank: $p<0.0001$), respectively. 10Y TFS differed significantly when comparing different features of CSPH. Patients with splenomegaly had a 10Y TFS of 74.0% whereas patients with oesophageal varices decreased to 59.5%. Hepatic encephalopathy as well as ascites were associated with an even worse prognosis (10Y TFS of 38.1% and 29.2%, respectively).

10Y overall survival (95.4% for the entire cohort) remained stable as long as patients remained compensated, but significantly declined in the setting of dACLD (10Y overall survival 66.7% log rank: $p<0.001$).

3.4 | Prognostic impact of different clinical and demographic characteristics on liver-related outcomes

Fifteen (11.5%) patients were identified as being incompliant, according to clinical documentation and elevated urinary copper excretion (24-h urinary copper concentration >100 μg/24 h or >500 μg/24 h during maintenance therapy with or without performing a 2-day drug holiday, respectively). In a cox regression analysis, we observed a slight numerical but not significant trend towards an increased risk of hepatic decompensation (HR 3.6; CI [95%]: 0.7–18.9; $p=0.1$), LTX or death (HR 1.7; CI [95%]: 0.4–7.9; $p=0.5$) in patients with insufficient adherence to treatment.

Thirty-nine (28.5%) patients showed neuropsychiatric symptoms as part of their clinical presentation. Interestingly, adherence to Wilson-specific treatment was not significantly different between patients with and without neuropsychiatric symptoms (OR: 1.39; $p=0.6$). In a cox regression analysis we further observed that the presence of neuropsychiatric symptoms was not associated with a significantly increased risk of hepatic decompensation (HR: 0.94; CI [95%]: 0.3–3.4; $p=0.9$), LTX or death (HR: 0.5; CI [95%]: 0.2–1.4; $p=0.2$).

We further observed that patients with male sex were numerically more likely to progress to hepatic decompensation (HR 2.0; CI [95%]: 0.5–7.8; $p=0.3$); however, statistical significance could not be proven, whereas the risk of being transplanted or dying (HR 0.8; CI [95%]: 0.3–1.8; $p=0.5$) was not significantly different between male and female patients.

However, we did observe, that the degree of liver disease severity at the time of diagnosis significantly increased the risk for the development of hepatic decompensation, LTX and death. Patients with cACLD at the time of diagnosis were more likely to progress to decompensated liver disease compared to patients without ACLD (HR: 3.8; CI [95%]: 1.0–15.1; $p=0.05$). In particular, patients with features of CSPH at the time of diagnosis were significantly more likely to progress to LTX or death compared to patients without CSPH (HR: 9.9; CI [95%]: 3.9–25.4; $p<0.001$). We further observed that patients with a higher MELD-Score at baseline, as an indicator for more advanced liver disease, were more likely to decompensate (HR 1.6 [per 1 point increase]; CI [95%]: 1.3–2.1; $p<0.001$), and to progress to LTX or death (HR 1.2 [per 1 point increase]; CI [95%]: 1.1–1.2; $p<0.001$). Similarly, we found that increased values of liver stiffness at diagnosis, measured by transient elastography, also indicated an increased risk for decompensation (HR: 1.1 [per 1 kPa increase]; CI [95%]: 1.0–1.1; $p=0.008$), LTX or death (HR: 1.1 [per 1 kPa increase]; CI 95%: 1.0–1.1; $p<0.001$).

3.5 | Prognostic significance of LSM and platelet count

Among patients with both, normal platelet count (≥150 G/L) and LSM <15 kPa, 10-Y cumulative decompensation rate was 2.6%. In contrast, patients presenting with either thrombocytopenia (<150 G/L) or LSM ≥15 kPa had a cumulative decompensation rate of 4% after 5 years and of 8.4% after 10 years of follow-up (log-rank: $p=0.002$; Tables 2 and 3; Figures 2 and 3).

Patients with both a normal platelet count and LSM <15 kPa had a 97.7% survival rate after 10 years, whereas WD patients presenting with thrombocytopenia and/or LSM ≥15 kPa showed a 10-year survival rate of only 83.9% (log-rank: $p=0.006$).

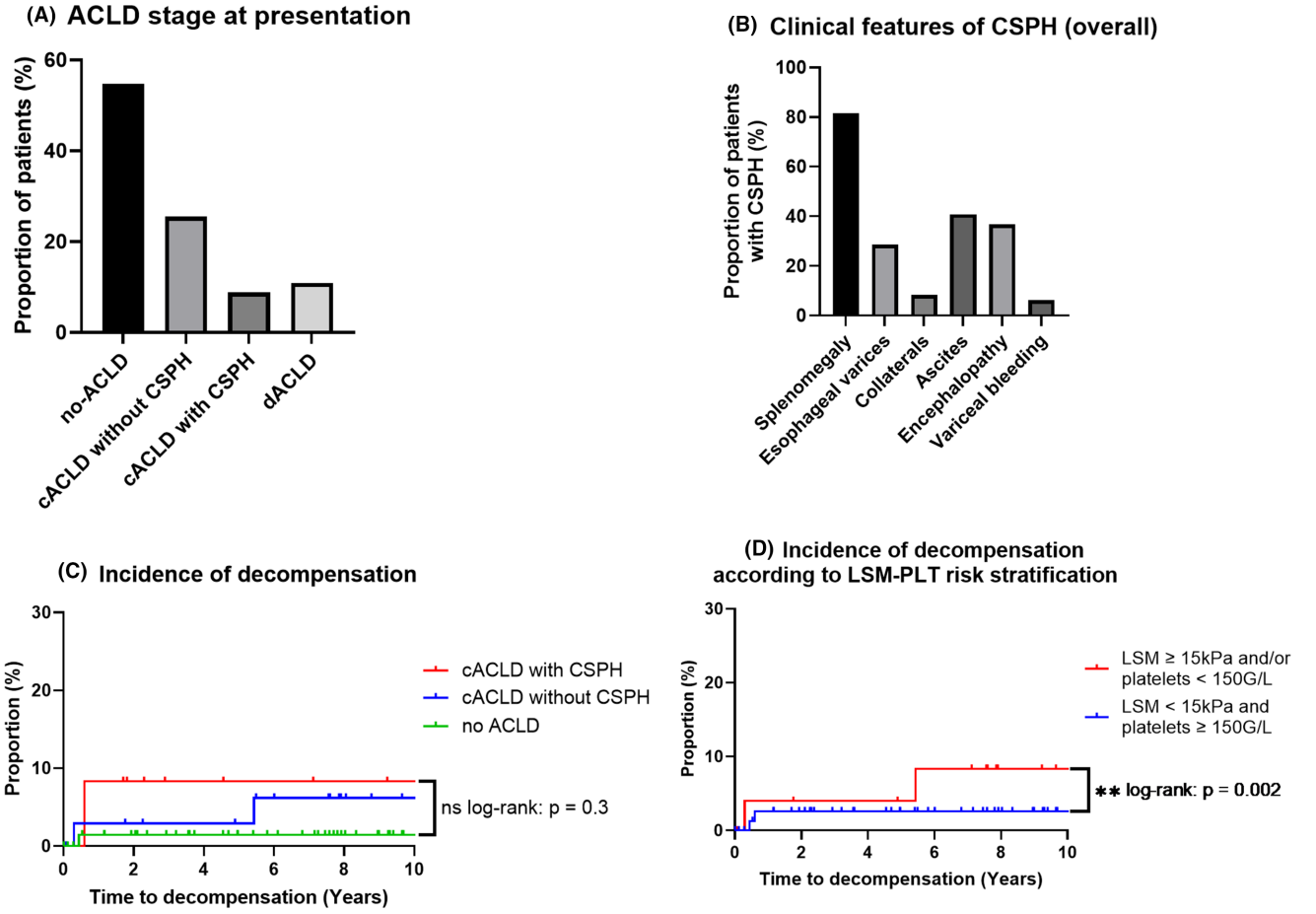

FIGURE 2 Prognostic value of ACLD stage and CSPH features in WD patients. (A) CLD stage at presentation. Data are depicted as percentages of the total number of WD patients included in this study. (B) Clinical features of CSPH (overall). Data on clinical features of CSPH (splenomegaly, varices, portosystemic collaterals, ascites, encephalopathy, variceal bleeding) are depicted as percentages of all patients diagnosed with CSPH ($n=49$). (C) Incidence of decompensation. 10-year cumulative incidence of decompensation in patients without ACLD, cACLD without CSPH and cACLD with CSPH (no ACLD vs. cACLD with CSPH: log-rank $p=0.3$). Data are depicted as Kaplan–Meier Plot. (D) Incidence of decompensation according to LSM-PLT risk stratification. 10-year cumulative incidence of decompensation in patients with LSM < 15 kPa and PLT ≥ 150G/L versus LSM ≥ 15 kPa and/or PLT < 150 G/L (log-rank $p=0.002$). Data are depicted as Kaplan–Meier Plot.

Liver biopsy was available in 88 (65.0%) patients. F0–F3 fibrosis did not impact on 10-year decompensation rate and TFS. Only patients with F4 fibrosis had an increased 5- and 10-year decompensation rate (12% and 16.4%, respectively; log-rank: $p=0.004$), which was mirrored by a decrease in 5- and 10-year TFS (67.8% and 64.4%, respectively; log-rank: $p<0.001$, respectively).

4 | DISCUSSION

About 50%–60% of all patients diagnosed with WD have been reported to show cirrhosis on liver biopsy,[10] while the incident-rate of ACLD at diagnosis in our WD cohort was 45.3%. In a Canadian study, including 48 WD patients, 63% were identified with clinical findings suggestive of CSPH of whom 26.7% progressed to hepatic decompensation over a median follow-up of 8.1 years.[18] In our WD cohort 19.7% of all patients were identified with clinical features of CSPH at diagnosis, whereas 16.1% developed CSPH features during their further course of disease. Among compensated (cACLD) WD patients with clinical features of CSPH at diagnosis ($n=12$), the cumulative incidence of decompensation was 8.3% after 10 years and, thus, lower compared to the Canadian cohort.

According to a previous study, the occurrence of severe hepatic events in non-ACLD patients with adequate adherence to WD-specific therapy seems rare[18] and also the tendency of fibrosis progression, assessed by transient elastography, only ranges between 5.6% and 8.5% throughout a 2-year follow-up period.[33] These data fit with our observation, that patients without ACLD at diagnosis are unlikely to progress to decompensation (10Y-incidence rate: 1.5%), LTX or death (10Y-TFS: 98.6%) while remaining under WD-specific pharmacotherapy. Accordingly, we observed that the severity of liver disease at baseline (based on MELD-Score, liver stiffness and presence of CSPH) had a significant impact on the progression to decompensated liver disease,

TABLE 3 Transplant-free survival according to distinct characteristics of patients with WD.

Variable	Liver transplant-free survival				N[a] total
	1 year	3 years	5 years	10 years	
Overall TFS	90.2%	89.4%	89.4%	88.3%	22 (16.1%)
Normal PLT count and LSM <15 kPa	97.7%	97.7%	97.7%	97.7%	2 (4.4%)
Thrombocytopenia (<150 G/L) or LSM ≥ 15 kPa	90.8%	87.7%	87.7%	83.9%	10 (30.3%)
Non-ACLD	98.6%	98.6%	98.6%	98.6%	4 (5.3%)
cACLD w/o CSPH	97.1%	97.1%	97.1%	93.6%	6 (17.1%)
cACLD with CSPH	91.7%	91.7%	91.7%	91.7%	1 (8.3%)
dACLD	33.3%	26.7%	26.7%	26.7%	11 (73.3%)
F0–F3	100%	100%	100%	100%	2 (4%)
F4	70.5%	67.8%	67.8%	64.4%	17 (44.7%)
Splenomegaly	80.0%	77.5%	77.5%	74.0%	16 (40%)
Oesophageal varices	78.6%	71.4%	71.4%	59.5%	6 (42.9%)
Variceal bleeding	66.7%	66.7%	66.7%	66.7%	2 (66.7%)
Hepatic encephalopathy	50.0%	44.4%	44.4%	38.1%	17 (94.4%)
Ascites	40.0%	35.0%	35.0%	29.2%	18 (90%)

Note: Transplant-free survival (TFS) according to distinct clinical characteristics after 1, 3, 5 and 10 years of follow-up. Patients were censored at the time of liver transplantation or death, whichever came first, leaving a total of $N = 22$ events.

Abbreviations: ACLD, advanced chronic liver disease, cACLD, compensated ACLD; dACLD, decompensated ACLD; CSPH, clinically significant portal hypertension; LSM, Liver stiffness measurement; PLT, platelets.

[a]Number of patients who died or received LTX (%) throughout the entire follow-up period.

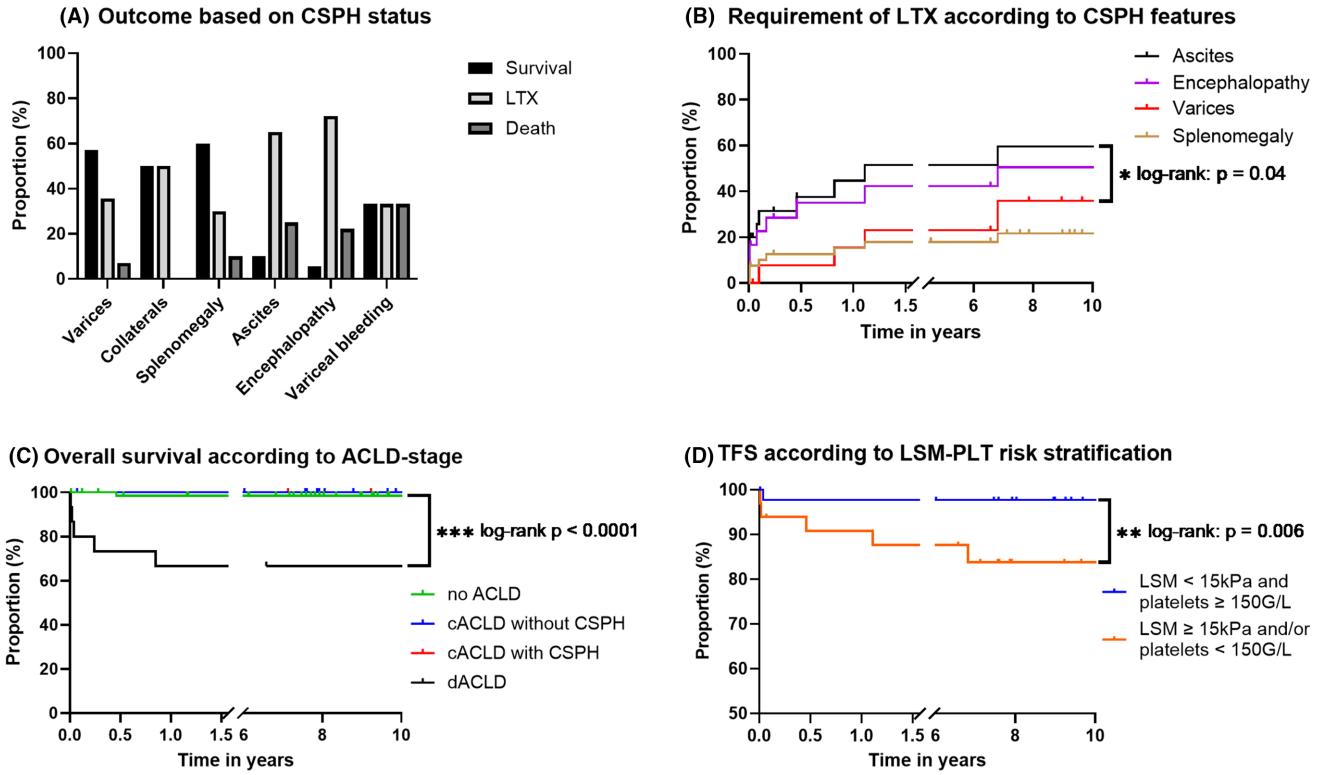

FIGURE 3 Rate of liver transplantation and survival according to ACLD stage and CSPH status. (A) Outcome based on CSPH status. Percentages of survival, LTX and death in different CSPH related features are depicted as bar charts. (B) Requirement of LTX according to CSPH status. This Kaplan–Meier Plot illustrates the cumulative incidence of liver transplantation in patients with different features of CSPH including splenomegaly, oesophageal varices, hepatic encephalopathy and ascites. (C) Overall survival according to ACLD stage. This Kaplan–Meier plot illustrates the overall survival according to the different ACLD stages, irrespective of whether patients had undergone liver transplantation or not (no ACLD vs. dACLD: log-rank: $p < 0.0001$). (D) TFS according to LSM-PLT risk stratification. This Kaplan–Meier plot illustrates the TFS in patients with LSM <15 kPa and PLT ≥150G/L versus LSM ≥15 kPa and/or PLT < 150 G/L (log-rank: $p = 0.006$).

LTX or death. In particular, patients with cACLD and features of CSPH at baseline were more likely to progress to decompensation despite ongoing WD-specific pharmacotherapy, when compared to patients without ACLD. Subsequently, the subset of WD patients with CSPH would likely benefit from additive portal hypertension treatment with NSBBs.[34]

Nevertheless, we would also like to highlight the importance of adequate WD-specific pharmacotherapy: In a sub-analysis of our WD cohort, including $n=45$ patients treated with zinc, d-penicillamine or trientine, who had paired LSMs (median interval 3.6 (IQR: 2.2–6.2) years), $n=16$ patients were classified as having cirrhosis (based on the previously published LSM cut-off at ≥9.9 kPa[33]). Of those, $n=10$ (62.5%) patients improved to non-cirrhotic thresholds, whereas $n=6$ (37.5%) showed no improvement.

Overall, 10Y-TFS in our retrospective WD cohort was high with 88.3%, which is comparable to preexisting literature.[35] However, the presence of CSPH in WD patients with cACLD significantly decreases TFS in comparison to patients without evidence of CSPH, which is further intensified in the setting of dACLD. Similar observations have been made in patients with other liver diseases as well[9] and underline the key prognostic importance of CSPH regarding hepatic decompensation and TFS.[34]

In this study we further observed that different CSPH related features have a distinct prognostic impact on liver related morbidity and TFS in patients with WD. On a clinical perspective, these findings underline the necessity to screen patients with WD for signs of CSPH using cross-sectional imaging, ultrasound, endoscopy and to further implement non-invasive surrogates[36,37] reflecting CSPH risk into clinical routine. Accordingly, the (repeated) use of LSM can provide valuable insights on disease progression and prognosis[33,38,39] with a LSM cut-off value of ≥10 kPa being highly indicative of cirrhosis in patients with WD.[33,40] For WD patients, specific recommendations regarding the interval between repetitive LSMs, are not available, however, based on our experience, we suggest performing LSM on a yearly basis. We additionally suggest a non-invasive algorithm that indicates an increasing risk for decompensation as well as an impaired TFS if either LSM is ≥15 kPa or PLT decrease to <150 G/L. This supports the clinical use of (repeated) LSM and platelet counts[30,31] as both hold important prognostic value for risk stratification, which is consistent with findings drawn from liver disease aetiologies, other than WD.[9]

A relevant limitation of this study is its retrospective design. Hence, Kaplan–Meier plots were used to estimate TFS and the cumulative incidence of decompensation. Additionally, we are aware that the number of patients with CSPH is relatively low. However, we believe that building up an even larger cohort of patients with Wilson's disease could only be performed through a multicentre approach, since only a minority of patients, receiving WD-specific pharmacotherapy, progresses to more advanced stages of liver disease.[33]

Furthermore, only $n=10$ (20.4%) patients with CSPH received non-selective beta-blockers (NSBBs) to reduce portal pressure. Particularly, only $n=5$ (35.7%) out of $n=14$ patients with oesophageal varices received NSBBs. The explanation for this observation is that our cohort was built up over a long period of time. Particularly during the early years of this cohort (especially before the land-mark study by Tripathi et al on NSBBs vs. EBL was published in 2009[41]), patients with oesophageal varices were more often referred to endoscopic band ligation. Patients with CSPH and NSBBs in the present study had a lower numerical risk of progressing to LTX or death, compared to patients with CSPH without NSBBs, but the difference was not statistically significant, and our study was also not primarily designed to assess this question.

The inclusion of splenomegaly as criterion for CSPH is controversially discussed since body height and CSPH-unrelated factors such as immune dysregulation have been reported to impact on spleen size.[42,43] Splenomegaly, however, is a generally accepted and frequent[44] clinical feature, that warrants further examination towards CSPH, if detected during routine imaging. Unfortunately, we were not able to measure HVPG in all our WD patients, which would represent the diagnostic gold-standard for CSPH diagnosis.[45] In turn, other CSPH-related features have been assessed in detail in all our WD patients, allowing clinicians to make prognostic estimations that support individualised follow-up and facilitate decision-making regarding CSPH screening and treatment. We further show that the combination of LSM and platelet count, as an easily available score, is of considerable prognostic value in the setting of WD, which allows for individualised care and may support early treatment intensification.

In conclusion, features of CSPH in patients with WD indicate a substantial risk for decompensation and impaired TFS. Splenomegaly was the most frequent feature of CSPH in patients with cACLD and ascites the most frequent first decompensating event. Progression of WD patients without ACLD at diagnosis to decompensation, transplantation or death is rare and, therefore, underlines the importance of adequate WD-specific pharmacotherapy. Non-invasive risk prediction based on LSM ≥15 kPa and/or thrombocytopenia (<150 G/L) serves as valuable surrogate for the risk of CSPH-related decompensation and mortality in patients with WD.

Clinicians should, therefore, monitor WD patients on a regular basis for features of CSPH. Considering that three out of eight deaths in our WD cohort were caused by CSPH-related complications, the use of non-selective beta-blockers and TIPS should be considered and further evaluated.

AUTHOR CONTRIBUTIONS

LB, PF, MM, MT, TR, AFS: Study concept and design. LB: Acquisition of data, Analysis and interpretation of data, Drafting of the manuscript and Statistical analysis. All authors involved in the critical revision of the manuscript for important intellectual content. AFS: Study supervision. All authors had access to the study data and reviewed and approved the final manuscript.

ACKNOWLEDGEMENTS

We dedicate this article to Prof Peter Ferenci (†) who laid the groundwork for this study and who always supported us with his advice and vast experience on Wilson's disease.

Declaration of personal interests: Dr Petrenko and Prof. Gschwantler declare no conflict of interest. Dr Burghart received travel support from Gilead. Dr Stättermayer consults for, advises, and/or is on the speakers' bureau for Boehringer Ingelheim, Gilead and MSD. Prof Mandorfer consults for, advises, is on the speakers' bureau for, and/or received travel support from AbbVie, Bristol-Myers Squibb and Gilead. He consults for, advises, and/or is on the speakers' bureau for W.L. Gore & Associates. Prof Trauner received grant support from Albireo, Alnylam, Cymabay, Falk, Gilead, Intercept, MSD, Takeda and UltraGenyx; honoraria for consulting from Abbvie, Albireo, Boehringer Ingelheim, BiomX, Falk, Genfit, Gilead, Hightide, Intercept, Jannsen, MSD, Novartis, Phenex, Pliant, Regulus, Siemens and Shire; speaker fees from Albireo, Bristol-Myers Squibb, Falk, Gilead, Intercept, MSD and Madrigal, as well as travel support from AbbVie, Falk, Gilead and Intercept. He is also co-inventor on patents on the medical use of norUDCA/norucholic acid filed by the Medical University of Vienna. Prof Reiberger received grant support from Abbvie, Boehringer-Ingelheim, Gilead, MSD, Philips Healthcare, Gore; speaking honoraria from Abbvie, Gilead, Gore, Intercept, Roche, MSD; consulting/advisory board fee from Abbvie, Bayer, Boehringer-Ingelheim, Gilead, Intercept, MSD, Siemens; and travel support from Boehringer-Ingelheim, Gilead and Roche.

FUNDING INFORMATION

None.

AUTHORSHIP

Guarantor of the article: Thomas Reiberger.

ORCID

Lukas Burghart https://orcid.org/0000-0003-3763-8473
Peter Ferenci https://orcid.org/0000-0003-2306-1992
Mattias Mandorfer https://orcid.org/0000-0003-2330-0017
Thomas Reiberger https://orcid.org/0000-0002-4590-3583

REFERENCES

Author names in bold designate shared co-first authorship.

1. European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56(3):671–85.
2. Gitlin JD. Wilson disease. Gastroenterology. 2003;125(6):1868–77.
3. Tao TY, Gitlin JD. Hepatic copper metabolism: insights from genetic disease. Hepatology. 2003;37(6):1241–7.
4. Lutsenko S, Petris MJ. Function and regulation of the mammalian copper-transporting ATPases: insights from biochemical and cell biological approaches. J Membr Biol. 2003;191(1):1–12.
5. Stremmel W, Meyerrose KW, Niederau C, Hefter H, Kreuzpaintner G, Strohmeyer G. Wilson disease: clinical presentation, treatment, and survival. Ann Intern Med. 1991;115(9):720–6.
6. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406–60.
7. Königshofer P, Hofer BS, Brusilovskaya K, Simbrunner B, Petrenko O, Wöran K, et al. Distinct structural and dynamic components of portal hypertension in different animal models and human liver disease etiologies. Hepatology. 2021;30:610–22.
8. Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2019;393(10181):1597–608.
9. Burghart L, Halilbasic E, Schwabl P, Simbrunner B, Stättermayer AF, Petrenko O, et al. Distinct prognostic value of different portal hypertension-associated features in patients with primary biliary cholangitis. J Gastroenterol. 2021;11:99–110.
10. Ferenci P, Stremmel W, Członkowska A, Szalay F, Viveiros A, Stättermayer AF, et al. Age and sex but not ATP7B genotype effectively influence the clinical phenotype of Wilson disease. Hepatology. 2019;69(4):1464–76.
11. Stättermayer AF, Traussnigg S, Dienes HP, Aigner E, Stauber R, Lackner K, et al. Hepatic steatosis in Wilson disease—role of copper and PNPLA3 mutations. J Hepatol. 2015;63(1):156–63.
12. Beinhardt S, Leiss W, Stättermayer AF, Graziadei I, Zoller H, Stauber R, et al. Long-term outcomes of patients with Wilson disease in a large Austrian cohort. Clin Gastroenterol Hepatol. 2014;12(4):683–9.
13. Członkowska A, Tarnacka B, Litwin T, Gajda J, Rodo M. Wilson's disease-cause of mortality in 164 patients during 1992-2003 observation period. J Neurol. 2005;252(6):698–703.
14. Bruha R, Marecek Z, Pospisilova L, Nevsimalova S, Vitek L, Martasek P, et al. Long-term follow-up of Wilson disease: natural history, treatment, mutations analysis and phenotypic correlation. Liver Int. 2011;31(1):83–91.
15. Merle U, Schaefer M, Ferenci P, Stremmel W. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. Gut. 2007;56(1):115–20.
16. Svetel M, Pekmezović T, Petrović I, Tomić A, Kresojević N, Ješić R, et al. Long-term outcome in Serbian patients with Wilson disease. Eur J Neurol. 2009;16(7):852–7.
17. Taly AB, Meenakshi-Sundaram S, Sinha S, Swamy HS, Arunodaya GR. Wilson disease: description of 282 patients evaluated over 3 decades. Medicine (Baltimore). 2007;86(2):112–21.
18. Moores A, Fox S, Lang A, Hirschfield GM. Wilson disease: Canadian perspectives on presentation and outcomes from an adult ambulatory setting. Can J Gastroenterol. 2012;26(6):333–9.
19. Lee BH, Kim JH, Lee SY, Jin HY, Kim KJ, Lee JJ, et al. Distinct clinical courses according to presenting phenotypes and their correlations to ATP7B mutations in a large Wilson's disease cohort. Liver Int. 2011;31(6):831–9.
20. Zhong HJ, Sun HH, Xue LF, McGowan EM, Chen Y. Differential hepatic features presenting in Wilson disease-associated cirrhosis and hepatitis B-associated cirrhosis. World J Gastroenterol. 2019;25(3):378–87.
21. Ferenci P, Pfeiffenberger J, Stättermayer AF, Stauber RE, Willheim C, Weiss KH, et al. HSD17B13 truncated variant is associated with a mild hepatic phenotype in Wilson's disease. JHEP Rep Innov Hepatol. 2019;1(1):2–8.
22. Ferenci P, Caca K, Loudianos G, Mieli-Vergani G, Tanner S, Sternlieb I, et al. Diagnosis and phenotypic classification of Wilson disease. Liver Int. 2003;23(3):139–42.
23. Schilsky ML, Roberts EA, Bronstein JM, Dhawan A, Hamilton JP, Rivard AM, et al. A multidisciplinary approach to the diagnosis and management of Wilson disease: 2022 Practice Guidance on Wilson disease from the American Association for the Study of Liver Diseases. Hepatology. 2023;1–49. Publish Ahead of Print. https://doi.org/10.1002/hep.32801
24. Frank K, Linhart P, Kortsik C, Wohlenberg H. Sonographic determination of spleen size: normal dimensions in adults with a healthy spleen. Ultraschall Med Stuttg Ger. 1986;7(3):134–7.

25. European Association for the Study of the liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145–72.
26. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII Faculty. Baveno VII—renewing consensus in portal hypertension. J Hepatol. 2022:959–74.
27. Scheiner B, Steininger L, Semmler G, Unger LW, Schwabl P, Bucsics T, et al. Controlled attenuation parameter does not predict hepatic decompensation in patients with advanced chronic liver disease. Liver Int. 2019;39(1):127–35.
28. Simbrunner B, Marculescu R, Scheiner B, Schwabl P, Bucsics T, Stadlmann A, et al. Non-invasive detection of portal hypertension by enhanced liver fibrosis score in patients with different aetiologies of advanced chronic liver disease. Liver Int. 2020;40(7):1713–24.
29. Bastati N, Beer L, Ba-Ssalamah A, Poetter-Lang S, Ambros R, Kristic A, et al. Gadoxetic acid-enhanced MRI-derived functional liver imaging score (FLIS) and spleen diameter predict outcomes in ACLD. J Hepatol. 2022;77(4):1005–13.
30. Schwabl P, Bota S, Salzl P, Mandorfer M, Payer BA, Ferlitsch A, et al. New reliability criteria for transient elastography increase the number of accurate measurements for screening of cirrhosis and portal hypertension. Liver Int. 2015;35(2):381–90.
31. Reiberger T, Ferlitsch A, Payer BA, Pinter M, Schwabl P, Stift J, et al. Noninvasive screening for liver fibrosis and portal hypertension by transient elastography—a large single center experience. Wien Klin Wochenschr. 2012;124(11–12):395–402.
32. Reiberger T, Püspök A, Schoder M, Baumann-Durchschein F, Bucsics T, Datz C, et al. Austrian consensus guidelines on the management and treatment of portal hypertension (Billroth III). Wien Klin Wochenschr. 2017;129(Suppl 3):135–58.
33. Paternostro R, Pfeiffenberger J, Ferenci P, Stättermayer AF, Stauber RE, Wrba F, et al. Non-invasive diagnosis of cirrhosis and long-term disease monitoring by transient elastography in patients with Wilson disease. Liver Int. 2020;40(4):894–904.
34. Mandorfer M, Simbrunner B. Prevention of first decompensation in advanced chronic liver disease. Clin Liver Dis. 2021;25(2):291–310.
35. Daniel-Robin T, Bénichou B, Leboucher C, Blein C, Combal JP. Epidemiology, treatment and burden of Wilson disease in France: a 10-year analysis of the national health insurance database. Clin Res Hepatol Gastroenterol. 2022;46(10):101992.
36. Reiberger T. The value of liver and spleen stiffness for evaluation of portal hypertension in compensated cirrhosis. Hepatol Commun. 2022;6(5):950–64.
37. Jachs M, Hartl L, Simbrunner B, Bauer D, Paternostro R, Scheiner B, et al. The sequential application of Baveno VII criteria and VITRO score improves diagnosis of clinically significant portal hypertension. Clin Gastroenterol Hepatol. 2023;21(7):1854–1863.e10.
38. Sini M, Sorbello O, Sanna F, Battolu F, Civolani A, Fanni D, et al. Histologic evolution and long-term outcome of Wilson's disease: results of a single-center experience. Eur J Gastroenterol Hepatol. 2013;25(1):111–7.
39. Semmler G, Jachs M, Mandorfer M. Non-invasive tests-based risk stratification: Baveno VII and beyond. Clin Mol Hepatol. 2023;29(1):105–9.
40. Karlas T, Hempel M, Tröltzsch M, Huster D, Günther P, Tenckhoff H, et al. Non-invasive evaluation of hepatic manifestation in Wilson disease with transient elastography, ARFI, and different fibrosis scores. Scand J Gastroenterol. 2012;47(11):1353–61.
41. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, Mcavoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology. 2009;50(3):825–33.
42. McKenzie CV, Colonne CK, Yeo JH, Fraser ST. Splenomegaly: pathophysiological bases and therapeutic options. Int J Biochem Cell Biol. 2018;94:40–3.
43. Terayama N, Makimoto KP, Kobayashi S, Nakanuma Y, Sasaki M, Saito K, et al. Pathology of the spleen in primary biliary cirrhosis: an autopsy study. Pathol Int. 1994;44(10–11):753–8.
44. Sakauchi F, Mori M, Zeniya M, Toda G. A cross-sectional study of primary biliary cirrhosis in Japan: utilization of clinical data when patients applied to receive public financial aid. J Epidemiol. 2005;15(1):24–8.
45. Reiberger T, Schwabl P, Trauner M, Peck-Radosavljevic M, Mandorfer M. Measurement of the hepatic venous pressure gradient and Transjugular liver biopsy. Jove J Vis Exp. 2020;160:e58819.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Burghart L, Ferenci P, Petrenko O, Mandorfer M, Schwarz M, Gschwantler M, et al. Portal hypertension and its prognostic implications in patients with Wilson's disease. Aliment Pharmacol Ther. 2024;00:1–10. https://doi.org/10.1111/apt.18060