

ORIGINAL ARTICLE

Effect of chelation therapy in pediatric Wilson's disease: Liver and endoscopic outcome

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Abstract

Background: As there is paucity of exclusive literature on pediatric hepatic Wilson's disease (WD), this study was undertaken to evaluate the efficacy of chelation on hepatocellular function and portal hypertension in WD.

Methods: Wilson's disease patients with ≥ 9 months of follow-up were evaluated for response to chelation therapy in the following categories: (a) complete remission, (b) partial remission (c) progression of disease; (d) drug toxicity. Pediatric end-stage liver disease (PELD), Nazar and New Wilson Index scores were compared. Hemodynamically stable patients underwent esophagogastroduodenoscopy (baseline and surveillance) and received prophylaxis (primary or secondary). Endoscopic outcome was assessed at follow-up.

Results: Of the 111 WD children (aged 9 [3–15] years; PELD score 16 [–11 to 60]), 65 with follow-up of 3.6 (0.8–12) years on chelation (83% D-penicillamine monotherapy, 17% D-penicillamine and zinc) were analyzed. 81% had severe disease at presentation. Favorable outcome (complete and or partial remission), progression of disease and drug toxicity were seen in 71%, 29% and 10.8%, respectively. Two-thirds had esophageal varices which did not show progression. Large esophageal varices (16%) were effectively downgraded in 3 (2–6) therapeutic endoscopic sessions. Nazar score and PELD score at baseline were independent predictors of outcome with favorable correlation with each other ($r = .864$, $P < .001$). PELD cutoff 9.45 (AUC: 71%, sensitivity: 87%, specificity: 50%; $P = .009$) and Nazar score cut off 3.5 (AUC: 68%, sensitivity: 83%, specificity: 50%; $P = .02$) were associated with poor prognosis.

Conclusions: Despite severe liver disease, the majority of hepatic WD can be managed on D-penicillamine monotherapy. PELD score and Nazar score effectively determine the outcome.

KEYWORDS

chelation, D-penicillamine, hepatic, pediatric, Wilson disease

1 | INTRODUCTION

Wilson disease (WD) is a hereditary autosomal recessive disease of copper metabolism.¹ Early diagnosis and treatment of WD is essential. Nazar and New Wilson Index (NWI) help in prognostication and triage of WD patients for liver transplantation.² D-penicillamine is an effective chelator, reduces liver inflammation, and improves synthetic functions. D-penicillamine is also postulated to inhibit liver and extrahepatic fibrogenesis.³ However, significant side effects and intolerance of D-penicillamine have been reported.^{4,6} Trientine, a safer chelator is not widely available globally. The role of zinc in advanced liver disease is not fully understood.^{5,7} Chelation therapy in WD requires sufficient time to effectively excrete the body copper and relieve target organs from oxidative stress.^{1,5} Biochemical responses and improvement in histological scoring require 6–9 months.^{5,8} Hence, the option of liver transplantation must be judiciously decided after having given an adequate time for chelation. Choice of chelation differs from center to center. As far as pediatric liver disease is concerned, there are many gaps in the management of advanced WD that remain unanswered. Since chelators take time to act for optimal response, is it justified to refer a patient urgently for liver transplantation? Can advanced or severe liver disease, be managed with a single chelating agent or is it necessary to combine two chelators? Exclusive pediatric literature addressing only hepatic manifestations of WD is scarce. We aimed to evaluate the outcome and effect of chelation therapy on the liver synthetic functions and portal hypertension in WD.

2 | METHODS

2.1 | Data retrieval

Clinical, biochemical, endoscopic and treatment data of children with WD (June 2007 to June 2018) in our department were retrieved from electronic records after institutional ethical clearance (IEC code 2017-223-IP-EXP). Confirmed cases of WD satisfying any two out of three criteria (serum ceruloplasmin <20 mg/dL by nephelometry, positive Kayser-Fleischer (KF) ring on slit-lamp examination, 24 hours urine copper >40 mcg/dL by atomic absorption spectrophotometry) were analyzed. Extrahepatic manifestations, sibling involvement and consistent liver histology (copper staining and/or copper associated protein positivity with or without steatosis) were ancillary to the primary criteria. Mutation analysis and hepatic copper estimation were not performed. Depending on the type of presentation, the cohort was classified as severe or stable disease and their profiles were tabulated. All stable patients underwent endoscopic evaluation for gastroesophageal varices within 4 weeks of presentation.

2.2 | Management of cases

As a departmental protocol, all patients were started on D-penicillamine and supportive therapy. Zinc was added if there was failure of clinical improvement to D-penicillamine within 4 weeks of starting therapy. Only asymptomatic patients with mild liver inflammation were started on zinc monotherapy. In case of drug intolerance at follow-up, chelators were changed accordingly. Dose of chelation was optimized as per clinical response, liver function test and 24 hours urinary copper.⁹ In those presenting with liver failure, end-stage disease or complications of cirrhosis, liver transplantation was advised. Those who did not opt for liver transplantation were continued on chelation and adequate supportive management.

2.3 | Evaluation of outcome

Effect of chelation was analyzed in two parts: (a) response to liver functions and (b) effect of portal hypertension based on endoscopic follow-up. Outcomes of varices were interpreted as surrogate response to liver fibrosis on chelation therapy. Those with follow-up of ≥ 9 months duration were evaluated for their response to chelation in the following categories: (a) complete response (CR) defined as asymptomatic patient meeting all three parameters: serum aspartate aminotransferase (AST) <2 \times upper limit of normal (ULN: 40 IU/L), serum albumin ≥ 3.5 g/dL and international normalised ratio (INR) < 1.5; (b) partial response (PR) defined as asymptomatic patient with any one of the three parameters: AST improvement from baseline up to >2 \times ULN (40 IU/L), albumin improvement from baseline up to <3.5 g/dL and INR improvement from baseline up to ≥ 1.5 ; (c) progression: deterioration of synthetic functions, decompensation or death; and (d) drug toxicity. To determine the prognostic factors of outcome at maximal follow-up, cohort was evaluated with the liver function test available at 3 weeks just after initial stabilization. They were divided into two groups: (a) good outcome (≥ 9 months follow-up with CR or PR) and (b) poor outcome (worsening liver synthetic functions, need for liver transplantation or death at any point in time). Those lost to follow-up and <9 months follow-up were excluded from the analysis of outcome. Prognostic scores such as pediatric end-stage liver disease (PELD), NWI and Nazar score were used in the analysis.¹

2.4 | Endoscopy protocol

Endoscopic grading for classification of varices used were Paquet's (esophageal varix size),¹⁰ Sarin (gastric varix location),¹¹ Hashizume (gastric varix size)¹² and Taor (portal

hypertensive gastropathy).¹³ Large esophageal varices (grade \geq II with red colour signs) were intervened by primary prophylaxis (endoscopic band ligation) in non-bleeders and secondary prophylaxis (endoscopic band ligation followed by 1% polidocanol sclerotherapy) in variceal bleeders. Small esophageal varices (grade I or II without red colour signs) were followed up and intervened if they enlarged. All patients underwent three weekly endoscopic sessions until esophageal variceal eradication (no varices or esophageal tags) followed by 6–12 monthly endoscopic surveillance.

2.5 | Statistical analysis

Statistical analysis was performed with SPSS 20 statistical software, USA. Data were expressed as median (range) and proportion. Continuous variables were compared with Mann–Whitney *U*-test, and qualitative data were compared with Chi-square test. Multivariate logistic regression analysis was performed to determine the predicting factors of poor outcome of chelation. Receiver operating curve (ROC) analysis was performed to determine the cut-off values of these predictive factors. Pearson's correlation was applied to assess correlation between independent predictors of prognosis. *P*-value <0.05 was considered as significant.

3 | RESULTS

3.1 | Baseline presentation at admission

Database of 111 WD children was retrieved. Clinical manifestations are shown in Table 1. Serum ceruloplasmin was 7.9 (2–19.3) mg/dL in 97% ($n = 108$). Ceruloplasmin levels <10 mg/dL was noted in 80% ($n = 89$) of patients. 24 hour urine copper was 312 (41–5000) μ g. 96% ($n = 106$) of patients had >40 μ g/day and 78% ($n = 86$) had >100 μ g/day. 83% ($n = 92$) had bilateral KF ring on slit-lamp examination. 63% ($n = 70$) met all three diagnostic criteria. Clinical presentations were classified as (a) severe ($n = 90$, 81%) comprising of decompensated chronic liver disease (CLD) [$n = 57$, 51.4%], acute liver failure (ALF) [$n = 17$, 15.3%], acute-on-chronic liver failure (ACLF) [$n = 16$, 14.4%]; (b) stable ($n = 21$, 19%) comprising of asymptomatic transaminitis [$n = 9$, 8.1%], compensated CLD [$n = 8$, 7.2%] and sibling screening [$n = 4$, 3.6%]. Table 2 shows the biochemical parameters, prognostic scores and outcome in patients with severe and stable WD.

3.2 | Overall hepatic outcome

Figure 1 flowchart shows the outcome of the entire WD cohort. Chelation was started in 109/111 patients at diagnosis.

TABLE 1 Clinical profile at time of diagnosis ($n = 111$)

Boys, % (n)	75% (84)
Age at onset of symptoms	8.8 (3–14.6) y
Age at diagnosis	9 (3–15) y
Duration lag of symptoms to diagnosis	2 (0.2–80) mo
Weight z-score <-2 SD, % (n)	21% (29)
Height z-score <-2 SD, % (n)	15% (17)
Clinical features, % (n)	
Jaundice	55.9% (62)
Ascites	52.3% (58)
Hepatomegaly	55.85% (62)
Splenomegaly	59.4% (66)
Hemolysis	21.6% (24)
Hepatic encephalopathy	18.9% (21)
Neurological involvement	10.8% (12)
Renal involvement	9.9% (11)
Peripheral stigmata of chronic liver disease	2.7% (3)
Variceal bleeding	1.8% (2)
Rickets	0.9% (1)
Prior sibling death/involvement	30.6% (34)
Consanguinity	1.8% (2)

Note: Renal involvement: microscopic hematuria—1, significant proteinuria—5, both (hematuria and significant proteinuria)—4 and renal tubular acidosis—1. SD, standard deviation.

Two patients died before chelation could be started. Chelators initiated were D-penicillamine monotherapy ($n = 89$; 82%), D-penicillamine and zinc combination ($n = 19$, 17%) and zinc monotherapy ($n = 1$). In the first hospital visit, 17 (15.3%) patients died and six were referred for liver transplantation elsewhere. All had severe liver disease. Of the 88 patients on chelators, 67 (76%) had severe liver disease and survived with native liver. Seventeen of 67 patients (decompensated CLD, $n = 10$, ACLF, $n = 5$, ALF, $n = 2$) were lost to follow-up after initial stabilization. All 21 with stable liver disease were available for follow-up. After excluding six patients with <9 months follow-up (decompensated CLD, $n = 5$, asymptomatic transaminitis [zinc monotherapy], $n = 1$), 65 patients with ≥ 9 months on chelation therapy (D-penicillamine, $n = 54$; D-penicillamine + zinc, $n = 11$) were analyzed for outcome. Total duration of follow-up of the 65 patients was 3.6 (0.8–12) years. Of this follow-up cohort, 53/65 patients (81%) had severe disease. Good outcome of chelation at maximal follow-up was seen 46 (70.8%) (CR [$n = 31$]; PR [$n = 15$]). The remaining 19 (29%) showed progression of liver disease and were counseled for liver transplantation. Table 3 shows response to chelation therapy according to liver disease presentation. Seven patients (10.8%) had D-penicillamine related side effects (sudden neurological deterioration, discoid skin rashes, glomerulonephritis and neutropenia). These patients

TABLE 2 Liver function tests and prognosis in different type of clinical presentation (n = 111)

Parameter	Severe disease (n = 90)			Stable disease (n = 21)					P-value
	Decompensated WD (n = 57)	ACLF (n = 16)	ALF (n = 17)	All cases of severe disease (n = 90)	Compensated WD (n = 8)	Asymptomatic transaminitis (n = 9)	Sib screening (n = 4)	All cases of stable disease (n = 21)	
Total serum bilirubin (mg/dL)	2.2 (0.29-3.6)	6.35 (1.8-54.6)	21.3 (2.8-53.2)	3.2 (0.3-54.6)	0.75 (0.3-1.4)	0.89 (0.32-1.4)	0.8 (0.6-0.9)	0.4 (0.3-1.47)	<.001
AST (IU/L)	136 (29-1900)	240 (74-932)	212 (90-760)	176 (29-1900)	51 (38-209)	97 (73-1641)	82 (49-258)	83 (38-1641)	.001
ALT (IU/L)	74 (26-2400)	81 (19-311)	60 (12-532)	74 (12-2400)	41 (23-107)	203 (105-1023)	86 (57-290)	107 (23-1023)	.188
Albumin (g/dL)	2.5 (1.1-3.6)	2.5 (1.7-3.4)	2.2 (1.5-3.5)	2.45 (1.1-3.6)	3.9 (3.5-4.2)	4.2 (3.5-5)	3.6 (3.5-4.5)	4 (3.5-5)	<.001
INR	2.2 (1.1-11)	3.3 (1.6-15)	5.2 (2.2-14.5)	2.7 (1.09-15)	1.3 (1.1-1.4)	1.1 (0.9-1.34)	1.1 (0.9-1.5)	1.1 (0.9-1.4)	<.001
ALP (IU/L)	271 (37-1297)	120 (22-602)	57 (9-510)	192 (9-1297)	370 (214-871)	386 (180-602)	276 (152-733)	379 (152-871)	.004
Hyponatremia, n (%)	9 (15.7%)	2 (12.5%)	8 (47%)	19 (21.1%)	0	0	0	0	—
PELD score	14 (−5 to 60)	23.5 (4-62)	41 (19-57)	20 (−5 to 62)	−4 (−10 to 4)	−7 (−11 to −4)	−9 (−10 to 0)	−7 (−11 to 4)	<.001
NWI score	7 (2-19)	11.5 (7 −18)	14 (9-20)	9 (2-20)	2 (1-4)	3 (1-9)	4 (2-9)	2 (1-9)	<.001
Nazar score	5 (0-12)	7.5 (4-12)	10 (6-12)	5 (0-12)	1 (0-4)	1 (0-4)	0 (0-3)	1 (0-4)	<.001
Mortality, n (%)	4 (7)	4 (25)	9 (53)	17 (19)	0	0	0	0	—
Liver transplantation, n (%)	6 (10.5)	0	0	6 (7)	0	0	0	0	—

Note: Data are presented as median (range). *P*-value indicates severe vs stable disease.

Abbreviations: ALCF, acute on chronic liver failure; ALF, acute liver failure; ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; GGT, gamma glutamyltransferase; INR, international normalized ratio; NWI, New Wilson Index; PELD, pediatric end-stage liver disease.

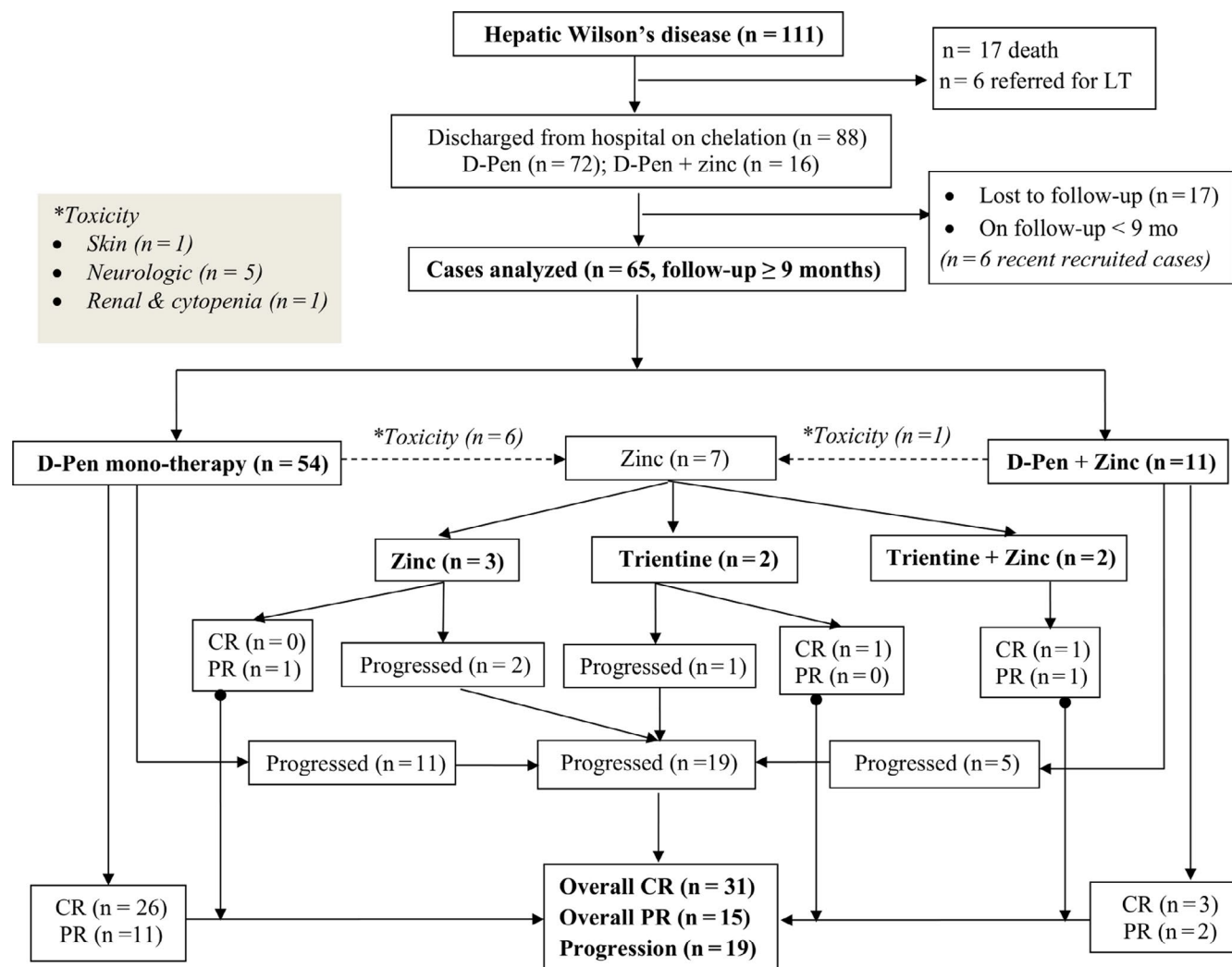


FIGURE 1 Flow chart showing outcomes of children with Wilson disease in the whole cohort. CR, complete remission; D-Pen, D-penicillamine; PR, partial remission

were changed over to zinc monotherapy (n = 3), trientine (n = 2) and combination of trientine and zinc (n = 2).

3.3 | Predictors of outcome

Table 4 shows the laboratory parameters and prognostic scores that predict good and poor outcomes. Of all the variables (albumin, total serum bilirubin, AST, INR, NWI, PELD score and Nazar score) that were entered into logistic regression analysis, only Nazar score ($P = 0.03$, OR: 8; 95% CI: 2.6-19) and PELD score ($P = 0.006$, OR: 23; 95% CI: 4.1-68) were found to be significant independent predictors of outcome. ROC analysis for predictors of poor outcome showed PELD cut-off 9.45 (AUC: 71%, sensitivity: 87%, specificity: 50%; $P = 0.009$) and Nazar score cut-off 3.5 (AUC: 68%, sensitivity: 83%, specificity: 50%; $P = 0.02$) as shown in Figure 2A. Kaplan–Meier

survival curves based on the cut-off values of PELD and Nazar score were computed for patients with good vs. poor outcome of therapy (Figure 2B,C). Correlation of PELD with Nazar score was $r = .864$, $P < .001$.

3.4 | Endoscopic outcome

Of the 111 patients, screening esophagogastroduodenoscopy was performed in 96 patients. Endoscopy was deferred in 15 hemodynamically unstable patients with advanced encephalopathy and multiorgan dysfunction. Large, small and no esophageal varices were present in 16% (n = 15), 49% (n = 47) and 35% (n = 34) patients, respectively. In those with large varices, endoscopic band ligation was performed (secondary prophylaxis; n = 2, primary prophylaxis; n = 13). All large esophageal varices were eradicated or downgraded to grade 1 over 3 (2–6) endoscopic sessions. None of the patients

TABLE 3 Effect of chelation therapy in subgroup of patients with ≥ 9 months follow (n = 65)

Type of presentation	Baseline PELD score	Baseline Nazar score	Initial chelation	Complete response (CR)	Partial response (PR)	Progression
Severe disease (n = 45)	16 (5-36)	4 (1-9)	DP (n = 25) DP + Z (n = 7)	13	7	12
ACLF (n = 7)	20 (4-32)	7 (3-12)	DP (n = 5) DP + Z (n = 2)	6	1	0
ALF (n = 6)	26 (19-41)	9 (6-11)	DP (n = 4) DP + Z (n = 2)	4	2	0
Stable disease (n = 20)						
Compensated CLD (n = 8)	-4 (-10 to 4)	1 (0-4)	DP (n = 8)	1	2	5
Asymptomatic transaminitis (n = 8)	-6 (-11 to -4)	1 (0-3)	DP (n = 8)	6	1	1
Sib screening (n = 4)	-9 (-10 to 0)	0 (0-3)	DP (n = 4)	1	2	1

Abbreviations: ACLF, acute on chronic liver failure; ALF, acute liver failure; CLD, chronic liver disease; DP, D-penicillamine; DP + Z, D-penicillamine + zinc; PELD, pediatric end-stage liver disease.

TABLE 4 Outcome at ≥ 9 months of chelation (n = 65)

Parameters	Good outcome (n = 46)	Poor outcome (n = 19)	P-value
Total bilirubin (mg/dL)	1.4 (0.4-10)	1.3 (0.5-7.1)	.44
INR	1.6 (0.9-3.1)	2.8 (1-3.8)	.92
Albumin (g/dL)	3.2 (1.8-5)	3.3 (2.2-4.43)	.82
AST (U/L)	107 (15-651)	93 (47-448)	.55
PELD score	4.4 (0-12.4)	8.6 (-0 to 28)	.008
Hemoglobin (g/dL)	11.3 (6-14.5)	10.4 (7.9-12.3)	.30
Platelet count ($\times 10^3$)	146 (50-490)	104 (40-375)	.05
NWI	4 (1-8)	4 (2-10)	.486
Nazar score	2 (0-5)	3 (0-7)	.025
Large esophageal varix (>grade 2) at diagnosis, n	1	8	<.001
Small esophageal varix at diagnosis, n	22	2	<.001
Gastric varix at diagnosis, n	3	4	.103

Note: Data are presented as median (range).

Abbreviations: AST, Aspartate aminotransferase; INR, international normalized ratio; NWI, New Wilson Index; PELD, pediatric end-stage liver disease.

(n = 15) had any interval bleeding, recurrence or re-bleeding from esophageal varices till longest follow-up. Of the 79 patients with small or no esophageal varices, 50 had follow-up of ≥ 9 months on chelation therapy. On follow-up endoscopy, none of the patients showed progression of esophageal varices. Primary gastric varices were present in the 15 patients with large esophageal varices (GOV1, n = 12; GOV2, n = 3 and IGV, n = 1). All were F1 (small) size and did not bleed. Primary gastric varices disappeared in seven and persisted in eight without enlargement in size until the longest follow-up. None of the patients required cyanoacrylate glue injection for gastric varices. Mild portal hypertensive gastropathy was present in 60% (n = 37) at baseline. Of this 37, portal hypertensive gastropathy disappeared in two-thirds and persisted in the rest at follow-up.

3.5 | Progression of liver disease in follow-up patients

Totally 19 (n = 12 severe; n = 7 stable) of 65 follow-up patients (29%) had progression of liver disease with recurrent hospital admissions (n = 16) and intercurrent systemic infections (n = 13). Among the 12 severe cases (baseline PELD 23 [12-36]), five (on D-penicillamine and zinc) developed complications (hepatopulmonary syndrome, n = 2;

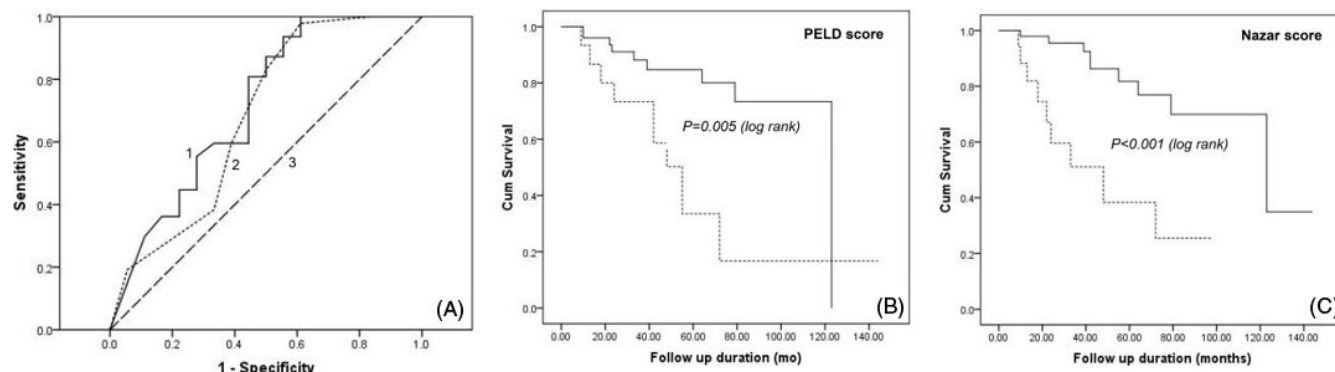


FIGURE 2 A, ROC curves of PELD and Nazar score for predicting poor outcome in children with Wilson disease. 1 = PELD (solid line), 2 = Nazar score (small dashed line), 3 = reference (large dashed line). B, C, Kaplan-Meier survival curves showing good (solid line) and poor (dashed line) outcome of therapy based on PELD (cut-off of 9.45) score (B) and Nazar score (cut-off of 3.5) (C)

renal insufficiency, $n = 2$, symptomatic coagulopathy, $n = 1$) after 14 (12–19) months of therapy. Seven patients (on D-penicillamine monotherapy) with severe disease developed recurrent ascites ($n = 3$), symptomatic hyponatremia ($n = 2$), hepatopulmonary syndrome ($n = 1$) and recurrent hemolysis ($n = 1$) after 24 (16–94) months of follow-up. Seven patients with initially stable disease (baseline PELD 2 [–2 to 6]) were on D-penicillamine monotherapy. Three patients were withdrawn from D-penicillamine by the neurologists due to sudden neurological worsening leading to suboptimal chelation and deterioration in liver functions. The remaining four showed features of decompensation (ascites and hepatic encephalopathy) after 18 (13–24) months of non-compliance (discontinuation, intermittent dosing or suboptimal doses) to therapy.

3.6 | Mortality

Seventeen patients with severe WD died in the first hospital admission before they could be referred for liver transplantation. They were aged 9 (6–14) years with PELD scores 46 (23–62), NWI 16 (11–19) and Nazar score 11 (5–12). Complications noted were advanced encephalopathy ($n = 11$), refractory ascites ($n = 7$), persistent hyponatremia ($n = 10$), acute renal failure ($n = 9$), severe pneumonia ($n = 5$), symptomatic coagulopathy ($n = 4$) and septicemia ($n = 10$). Ascitic fluid infection was seen in six patients (*Escherichia coli*, $n = 4$; coagulase negative *Staphylococcus aureus*, $n = 1$; *Burkholderia cepacia*, $n = 1$).

4 | DISCUSSION

The challenges in WD are multifold as the disease has a wide spectrum of age presentation and involvement can be multi-systemic. This study reports the hepatic presentation

in a large pediatric cohort and its outcome over a median and maximum span of 3.5 and 12 years, respectively. The management protocol was uniform as D-penicillamine was the first drug of choice in all patients. Hence there was no heterogeneity in interpretation of outcome with respect to chelation therapy. Our experience also provides an insight into the degree of portal hypertension in this disease.

Hepatic manifestations of WD are mostly encountered in children as shown by Walshe et al¹⁴ by age-phenotype effect. In our study, decompensated CLD was the most common presentation (51%) similar to other series.¹⁵ ALF was seen in 15% in our series much lower (27%–47%) than those reported elsewhere.^{16–18} We found intravascular hemolysis in 21.6% in total cohort, specifically in 68.7% of patients with ALF. Varying prevalence of hemolysis is well known from 3.5% to 30% in pediatric experience and 16.6% in adults.^{1,19–23} ACLF was seen in 14% of our patients. Our center had earlier shown that 41% of ACLF was due to WD and the majority of them had hepatitis E as an acute insult.²⁴ 39% WD who presented as ALF ($n = 16$) or ACLF ($n = 17$) had improved in our study with native liver. As compared to our result, Thanapirom et al showed 64% improvement in WD with ALF and ACLF.²⁵ 97% had low serum ceruloplasmin possibly due to lower albumin in severe liver disease. Remarkably 82% of our hepatic cohort had KF ring positivity. In future, it would be interesting to compare and study the phenotype-genotype differences with other ethnicities.

An important feature in our study was that despite the interval of presentation (median 2 months lag from symptom to diagnosis), the majority (81%) had severe liver disease, most of whom had decompensated CLD. Markers of severe disease were poor synthetic functions (total bilirubin, albumin and coagulation), hyponatremia and AST levels. All the prognostic scores (NWI, Nazar and PELD) were significantly higher in the severe disease. A median PELD score of 20 in severe disease would naturally merit enlistment for liver transplantation at the very onset. However, the challenge and only option in

a non-transplant setting was to manage optimally with medical therapy and salvage the majority. A physician's choice of chelating drug is based on the stage of disease, concomitant neurological involvement and compounded by daunting adversities. Hence, the choice of chelation differs from center to center and no guidelines clearly recommend one drug over the other.^{2,5,9,26} D-penicillamine is a very effective chelator as compared to trientine and zinc. In our cohort, where the majority had severe WD with high body copper load (median urinary copper 312 µg/day and 82% KF ring positivity), the choice of chelation was justifiably D-penicillamine. Zinc was added as second line dual therapy selectively in those who failed to show optimal response to D-penicillamine with the hope of rapid synergistic chelation and quicker liver recuperation. Dual therapy is often chosen in dire and desperate circumstances when disease is severe and progression is precipitous. A small case series showed improvement of decompensated WD with combination of D-penicillamine or trientine with zinc in five children who otherwise required liver transplantation.²⁷ Unlike prompt response in other treatable liver diseases such as autoimmune liver disease (immunosuppression) and chronic viral hepatitis (antiviral therapy), chelators in WD work slowly with best effects appreciable after 6-12 months of therapy.^{6,8} Hence, we chose to study the outcome of those patients who have received at least 9 months of chelation. In the follow-up cohort (n = 65) of patients, 70.8% of entire follow-up cohort and specifically 73.3% of severe disease could be salvaged. The majority of them were on D-penicillamine monotherapy. The reported efficacy of chelation in well-designed studies in literature varies from 50%-66.6%.^{1,19,20,27-30} In milder hepatic WD, the reported efficacy with D-penicillamine is 79%-90%.^{4,6} In our study, the indicators of poor outcome were PELD score (cutoff >9.45) and Nazar score (cutoff >3.5) with fairly reliable ROC with AUC of 0.71 and 0.68, respectively. Based on these two prognostic scores, the survival curves provided significant results. Devarbhavi et al¹⁸ showed similar AUC results of PELD and Nazar score for predicting mortality in children with WD who presented with ALF. The reasons for progression of disease in severe cases could have been multifactorial. It would be prudent to assess body copper load, degree of fibrosis, volume of residual liver parenchyma and immune functions in future prospective studies on WD. Progression of stable disease in our cohort was due to D-penicillamine intolerance, suboptimal chelation and poor long term adherence.

No doubt, liver transplantation must be promptly considered in those with rapidly failing liver functions, complications of cirrhosis or life-threatening adversities of chelators. Ohya et al reported eight WD patients who were referred for liver transplantation for liver failure and

cirrhosis. Three of the four who did not have a suitable donor continued to survive with native liver on optimal chelation. The indications of liver transplantation in the other cases were liver atrophy, severe leucopenia due to D-penicillamine and hepatic rickets.³¹ Kido et al, similarly reported three of five WD children who survived with native liver despite high PELD and NWI. The other two underwent liver transplantation due to variceal bleeding and progressive encephalopathy.³² As a desperate measure, chelation was initiated in all cases of ACLF and ALF with a hope of survival in our study. Despite 13 patients showing improvement at follow-up, we acknowledge that 13 of our 33 patients with ACLF or ALF died at the onset. The reasons were finances for transplantation, non-availability of donor, unstable general conditions and overwhelming systemic complications. When a pediatric Wilson's disease patient presents with liver failure, immediate consultation or referral to a liver transplantation facility is critical to carefully evaluate the indication for lifesaving emergent liver transplantation.

A minority of WD patients in our cohort were variceal bleeders (1.8%). Large unbled varices were found in 16% that required primary prophylaxis, more in the poor outcome group. The rest of the esophageal varices and gastric varices did not show progression on chelation therapy nor did they re-bleed. Interestingly, our patients despite severe liver disease in 80% and poor outcome in 29%, did not show progression of gastroesophageal varices. The majority remained eradicated or small sized varices. These patients were not on beta-blockers. In light of the known antifibrotic activity of chelators, would WD patients have lesser degree of portal hypertension? This question can be prospectively addressed if hepatic venous pressure gradient is measured in WD and compared to non-Wilsonian cirrhotics. Whether D-penicillamine has any effect on reversal of fibrosis could be addressed in larger studies that evaluate liver elastography, follow-up liver histology and profibrotic-antifibrotic tissue markers.

Our study had a few limitations. This was a non-transplant center experience. Despite the large number of cases, a significant proportion was lost to follow-up from the initial diagnosis. Our modest experience was centered around the usage of D-penicillamine and not other chelating agents. Baseline and follow-up liver elastography would have been augmentative to our results.

In conclusion our study shows that the majority of pediatric hepatic WD can be safely managed with D-penicillamine monotherapy despite severe liver disease. PELD score and Nazar score effectively determines the outcome. Patients with severe liver disease who initially present with liver failure and those who do not recover during follow-up may qualify for liver transplantation and timely evaluation is critical.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

MCD: analysis and interpretation of the data; primary drafting of the article. MSS: conception and design; final drafting of the article; critical revision of the article for important intellectual content; final approval of the article. AS: study supervision; important intellectual inputs. SKY: conception and design; important intellectual inputs. UP: study supervision.

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