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ORIGINAL ARTICLE

AARC-ACLF score: best predictor of outcome in children and adolescents with decompensated Wilson disease

Seema Alam[1] · Bikrant Bihari Lal[1] · Vikrant Sood[1] · Rajeev Khanna[1] · Guresh Kumar[2]

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Abstract

Background and aims Doubts have been raised about efficacy of New Wilson's index (NWI) in predicting Liver Transplant (LT) or mortality in decompensated Wilson Disease (WD) patients. APASL ACLF Research Consortium (AARC) has introduced a new score (AARC-ACLF) which has not been studied in children.

Methods Data of all pediatric WD cases were prospectively collected and analyzed. Cox regression and Area Under Receiver Operative Curve (AUROC) analyses were used to identify best predictive score for mortality at 90 days.

Results Sixty-six confirmed cases of decompensated WD, 39 (59%) improved on medical management and 27 (41%) either died (20) or were transplanted (7). Among those with NWI ≥ 11 (42/66 cases) 19 survived versus those with NWI < 11 (24/66), 4 died. NWI (HR 1.23, 95% CI 1.07–1.42, $p = 0.005$), AARC-ACLF (HR 1.66, 95% CI 1.34–2.05, $p = 0.000$) and Chronic Liver Failure-Sequential Organ Failure Assessment score also known as CLIF–SOFA (HR 1.31, 95% CI 1.13–1.50, $p = 0.000$) were all significantly associated with death on univariate Cox regression analysis. On comparative evaluation of the predictive scores in the present cohort, the highest positive (6.02) and lowest negative (0.09) likelihood ratios as well as highest accuracy (87.88%) revealed AARC-ACLF as the best predictor of mortality. AARC-ACLF had the best predictability with AUROC of 0.939 and the minimum standard error of 0.027. For every unit increase in AARC-ACLF score, there is likelihood of 66% increase in 90 day mortality. The optimal cutoff for the AARC-ACLF score to predict mortality was 11 or more.

Conclusion AARC-ACLF is the best score for the prediction of mortality at 90 days in decompensated WD cases.

Keywords Wilson's disease · Wilson · Hepatic encephalopathy · Plasmapheresis

Introduction

Wilson disease (WD) is an autosomal recessive disorder where incorporation of copper into the hepatic ceruloplasmin is impaired. The gene defective in WD, ATP7B, codes for a copper-transporting ATPase [1]. WD is one of the few treatable metabolic liver diseases where prognosis depends on early institution of chelation therapy before irreversible damage occurs. In 1986, Nazer prognostic score (based on AST, bilirubin and INR) was derived with 34 children and adult cases of WD and further validated in 9 cases [2]. Two decades later, the same unit used data from 74 retrospectively enrolled children with WD to derive New Wilson index (NWI) with 2 added factors (WBC and Albumin) to the old score [3]. NWI was further validated in 14 prospectively enrolled children in the same study. Based on the current evidence, chelation therapy is mandatory for both decompensated and compensated WD. Further for fulminant

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✉ Seema Alam
seema_alam@hotmail.com

Bikrant Bihari Lal
bikrant18may@gmail.com

Vikrant Sood
drvickyster@gmail.com

Rajeev Khanna
drrajeev_khanna@rediffmail.com

[1] Department of Pediatric Hepatology, Institute of Liver and Biliary Sciences, New Delhi 110070, India

[2] Institute of Liver and Biliary Sciences, New Delhi, India

WD, liver transplantation (LT) is needed if the NWI is ≥ 11 [3]. Some of the researchers [4] have raised doubts about the efficacy of NWI in decision-making for LT. Pediatric/Medical end-stage liver disease (PELD/MELD) Scores and the predictive model derived in an Indian study labeled as HD score using the initials of the first author [5] have been described as prognostic markers. WD is the most important cause of pediatric acute-on-chronic liver failure (ACLF) [6–10]. Chronic liver failure Sequential organ failure assessment (CLIF–SOFA) is an ICU score used to predict mortality in ACLF in Europe. CLIF consortium has developed the CLIF–SOFA score for assessing disease severity and prognostication in ACLF as defined by European association of study of liver disease (EASL) [11]. More recently, APASL ACLF Research Consortium has derived AARC-ACLF score [12] to prognosticate ACLF and has been further validated in children [10]. After the institution of the mandatory chelation for all cases, there is a need to identify prognostic markers, to consider LT early in the course of the disease, for best results. This work was thus planned to study the predictive risk scores for mortality at 90 days in decompensated WD in children and adolescents.

Methods

The study includes data of all patients presenting to Pediatric Hepatology department (age < 18 years) between January 2011 and July 2018 with liver disease. All underwent detailed etiologic work up including viral, autoimmune, metabolic, vascular, and histological evaluation as applicable. All patients were screened for common causes of hepatitis such as viral hepatitis (Hepatitis A, B, C, and E), autoimmune hepatitis and drug-induced liver injury by appropriate evaluation. Diagnosis of WD was based on Leipzig score [13]. Positive mutational analysis (1 homozygous or 2 heterozygous) for the 5 common and known Indian mutations of WD (c.448_452del; p.Ile1102Thr (3305 T > C); p.Cys271 (813 C > A), p.Gly1061Glu (3182 G > A); c.1708-1G > C) was also done. The Serum ceruloplasmin and urinary copper estimation were performed by nephelometric method (Dade Behring BN ProSpec system) and atomic absorption spectrophotometry, respectively. KF ring evaluation by slit lamp was done by a single experienced ophthalmologist. For those with no hepatic encephalopathy (HE) or HE grade 1/2, slit lamp was performed at admission. For HE grade 3 or 4, the KF ring was seen on torch light or/and later confirmed with slit lamp examination once the HE improved.

HE grading was done as per the West Haven Classification [14]. It was considered essential to rule out all other causes of chronic liver disease, since ceruloplasmin can be falsely low due to liver failure and urinary copper can be increased in other etiologies. Decompensation was considered as presence of jaundice, ascites and/or encephalopathy. All the rest were considered compensated. ACLF was defined as per the Asian Pacific Association for the Study of the Liver (APASL) including those with no prior decompensation [15]. All the decompensated cases not fulfilling the criteria for ACLF were labeled as chronically decompensated chronic liver disease (DCLD). Since all our WD cases presenting as acute/fulminant liver failure had evidence of underlying chronic liver disease (based on abdominal imaging or liver biopsy), they were labeled as ACLF as reported earlier [6]. The clinical and laboratory data (including serum bilirubin, serum transaminases, serum albumin, international normalized ratio/INR, hemogram, lactate etc.) were prospectively collected. In children fulfilling the definition of ACLF, acute precipitating event was labeled as "Wilsonian flare" if no viral infection or hepatotoxic drug intake was recognized as the acute event. The concept of Wilsonian flare has only been used in ACLF and not in DCLD where, by virtue of definition, an acute decompensation is absent.

Patients were managed with a combination of D-pencillamine (20 mg/kg/day in two divided doses) and zinc acetate (as elemental zinc in dose of 75 mg/day in < 50 kg body weight and 150 mg/day in > 50 kg body weight in two divided doses) given 5–6 h apart from each other. The practice at our centre is to educate the parents to follow the rule of 6 am and 6 pm doses for D-pencillamine and 11 am and 11 pm doses for Zinc. This has now been recommended for decompensated WD by the ESPGHAN 2018 guidelines too [16]. In all patients, D-pencillamine was started at the dose of 10 mg/kg/day and increased to 20 mg/kg/day in a week's time while monitoring for side effects and tolerance. All patients with the HE grade 3 and 4 received mechanical ventilation. Ammonia scavengers, antibiotics, anti-fungals, diuretics, intravenous fluids and oral/nasogastric feeds were given as and when indicated. Since 2015, as per protocol, at least 3 consecutive cycles of high volume plasma exchange (HVPE; with 1.5–2 times of plasma volume) were done for selected patients along with standard treatment. The indications for HVPE were NWI ≥ 11, hemolysis and deteriorating HE grade. INR trends post the cycle of plasmapheresis were followed for assessing improvement/deterioration.

Survival without LT was improvement of decompensation, i.e., ascites, icterus, and hepatic encephalopathy after ensuring compliant medical therapy. The patients were discharged from hospital after they recovered from complications like shock, spontaneous bacterial peritonitis, encephalopathy, respiratory embarrassment due to ascites and/or acute kidney injury. Death or LT by 90 days after admission was recorded. NWI and Pediatric/Medical end stage liver disease (PELD/MELD) scores were calculated prospectively but the predictive model derived in an Indian study labeled as HD score using the initials of the first author [5], AARC-ACLF and CLIF–SOFA were calculated retrospectively

from the parameters at admission. Follow-up was done every 1–2 weeks till the decompensation (e.g., jaundice, ascites, and coagulopathy) resolved and thereafter the patients were assessed monthly.

Statistical analysis

Statistical analysis was performed with SPSS version 23. To identify significant differences between the two groups, univariate Cox regression analysis (CRA) was performed. All quantitative variables were expressed as median and Inter Quartile range (IQR) between 25th and 75th percentiles. The continuous data of the five indices were entered into receiver-operating curve (ROC) analysis and the area under the receiver-operating curve (AUROC) was calculated to compare the predictive accuracy of the various indices. With the objective to reach the AUROC above 0.80 with minimum possible standard error, we chose all those AUROC higher than 0.80 and standard error below 0.50, for further examination. To calculate cutoff values, the optimal sensitivity and specificity were selected. The indices calculated at admission were used for predictive analysis and all the events (deaths) completed by 90 days were included.

Results

Of the 659 chronic liver diseases (CLDs) patients admitted in the study period, 125 (81 males, 64.8%) suspected cases of WD reported to this centre between Jan 2011 and July 2018, with presentation of ACLF (46) and DCLD (40) in 86 cases and compensated CLD in 39 cases. The median age of this cohort was 108 months (range 39–225 months). There were additional 10 asymptomatic siblings diagnosed as WD on screening whose median age was 46 months (range 19–68 months) (Fig. 1). Of the 39 compensated CLD, 10 were already on treatment for WD and improving. Nineteen (15.8%) of the 125 symptomatic cases had associated extrapyramidal involvement, e.g., motor rigidity, tremors, mask-like facies, dysphagia, and gait abnormalities with dyskinesia.

Of the total 86 suspected decompensated WD cases, 66 (76.6%) could fulfill the Leipzig criteria for diagnosis of WD. There were 44 (66.7%) males and 22 (33.3%) females in this cohort. KF ring was present in 60 (90.9%) patients in this cohort. Forty-seven (71.2%) cases had serum ceruloplasmin ≤ 10 and only one case had urinary copper < 100 µg/day. Six (9.1%) of the 66 decompensated WD cases had associated extrapyramidal involvement, e.g., motor rigidity, tremors, mask-like facies, dysphagia, and gait abnormalities with dyskinesia We could perform the set of 5 known mutations for 25 patients in this cohort due to logistic constraints and 14 showed positivity for at least one of the mutations. There

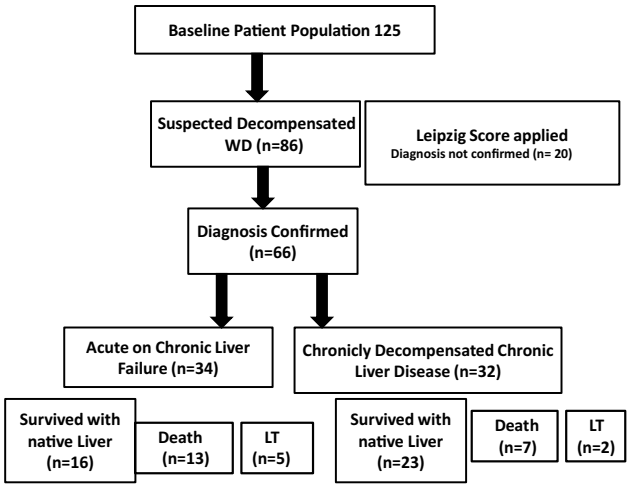


Fig. 1 Flow diagram of the cohort of decompensated Wilson disease

were 34 ACLF and 32 DCLD cases in this decompensated WD cohort. All ACLF and 23 DCLD were treatment-naïve at admission. The remaining 9 DCLD were started on management for WD and referred to us for LT.

Presentation and outcome of the decompensating WD

Jaundice was the presenting symptom in all of the ACLF and 14 (43.75%) of the DCLD. Twenty-four of the 32 DCLD cases had bilirubin below 5 mg/dl at admission. Median bilirubin at admission in ACLF cases was 22.95 mg/dl (IQR 7.4–30.82 mg/dl) with 19/34 having bilirubin levels ≥ 20 mg/dl. HE at admission was present in 45 (68.2%) of 66 cases: 32 cases had HE grade 1 or 2 and 13 had HE grade 3 or 4. HE grade 3 or 4 was present in 9/34 (20.5%) of ACLF and 4/32 (12.5%) of DCLD and the difference was not significant (OR 2.52 95% CI 0.69–9.2, $p = 0.22$). Median values of bilirubin, INR, NWI, HD score, CLIF–SOFA and AARC-ACLF were significantly higher in ACLF cases whereas liver atrophy was seen in significantly higher numbers among DCLD cases (Table 1). Of the 34 children with ACLF, acute precipitating event was "Wilsonian flare" in 21 (61.8%), hepatitis A viral infection in 10 (29.4%), hepatitis E viral infection in 2 and complimentary/alternative medication use in 1. Number of Coomb's negative hemolysis was comparable: 24 in ACLF versus 16 in DCLD (OR 2.40, 95% CI 0.87–6.60, $p = 0.130$).

Of the total 66 WD-decompensated cases 39 (59%) improved on medical management and 27 (40.9%) either died (20, 30.3%) or were transplanted (n = 7) within 90 days of the diagnosis (Fig. 1). One patient who died of empyema 6 months after ACLF resolved was considered as having survived. Unavailability of donor (6), negative consent for LT (8) and logistic constraints (6) were the

Table 1 Comparison of clinical and biochemical profile of ACLF versus DCLD among patients with WD

Variable	ACLF ($n=34$)	DCLD ($n=32$)	Effect size	95% CI	p value
HE grade 3–4 (n)	9	4	2.52[b]	0.69–9.2	0.22
Hemolysis (n)[a]	24	16	2.40[b]	0.87–6.60	0.130
Ascites (n)	30	25	1.73[b]	0.44–6.8	0.505
Liver atrophy (n)	5	17	0.15[b]	0.05–0.45	0.001
BMI z score	− 0.5 ± 1.4	− 1.2 ± 1.4	0.7[c]	− 0.1 to 1.4	0.083
Bilirubin (mg/dl)	23.7 ± 16.1	4.4 ± 4.7	19.3[c]	13.3–21.5	< 0.0005
INR	3.5 ± 1.2	2.5 ± 0.9	1[c]	0.4–1.5	0.001
TLC (/mm^3)	14.8 ± 8.1	8.1 ± 4.5	6.7[c]	3.3–10.1	< 0.0005
Albumin (g/dl)	2 ± 0.6	2.2 ± 0.5	0.1[c]	− 0.4 to 0.2	0.438
Ceruloplasmin (mg/dl)	9.4 ± 4.5	7.6 ± 4.8	1.8[c]	− 0.5 to 4.3	0.128
24 h urinary copper µg/24 h	944 ± 747	614 ± 515	330[c]	− 10 to 669	0.057
NWI	14.7 ± 2.9	9.7 ± 3.1	5[c]	3.5–6.6	<0.0005
HD score	27.6 ± 17.5	6.2 ± 5.7	21.4[c]	14.5–28.2	<0.0005
PELD	31.5 ± 7.7	18.6 ± 8.3	12.9[c]	8.7–17	<0.0005
CLIF–SOFA	10.5 ± 3.6	7.5 ± 3	3[c]	1.3–4.7	0.001
AARC-ACLF	10.9 ± 2.8	8.2 ± 2.3	2.7[c]	1.4–4.1	<0.0005

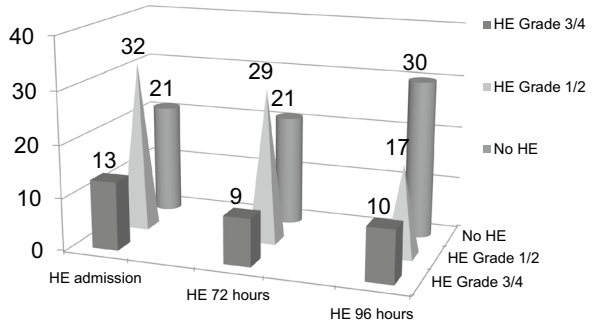
ACLF acute-on-chronic liver failure, *DCLD* decompensated chronic liver disease, *WD* Wilson's disease, *HR* hazard ratio, *95% CI* 95% confidence interval, *HE* hepatic encephalopathy, *BMI* Body Mass Index, *TLC* total leukocyte count, *INR* international normalized ratio, *PELD* Pediatric Endstage Liver Disease Score. *CLIF–SOFA* chronic liver failure-sequential organ failure assessment, *AARC-ACLF* APASL ACLF research consortium score for ACLF

[a]Coomb's negative, *Median (IQR)

[b]Odds ratio

[c]Mean difference

common causes for death without LT. Eight children died within 7 days and rest within 8–90 days. The median time to death was 12 (range 1–89) days from presentation. Six children were transplanted within 96 h and the 7th child was transplanted on 35th day of admission. Among those with NWI ≥ 11 (42/66 cases) 19 survived, 16 died and 7 received LT versus those with NWI < 11, 20 survived and 4 died with none receiving LT. Of the 39 survivors with native liver, 3 presented with HE grade 3/4, 18 with HE grade 1/2 and 18 with no HE. Among the 20 patients who died, 5 presented with HE grade 3 or 4, 12 with HE grade 1 or 2 and 3 with no HE. Ten cases of HE grade 1 or 2 and 1 case of no HE were showing signs of deteriorating HE within 24 h of admission. The 3 cases with no HE at admission who eventually died were having NWI of 6, 14, and 17, respectively. Among those who were transplanted, 5 presented with HE grade 3 or 4 and 2 with HE grade 1 or 2 (Fig. 2). Sixteen patients received 54 HVPE cycles (median number of cycles being 3). Twelve cases underwent ≥ 3 cycles of HVPE each: 4 survived with native liver, 6 patients survived for 11–89 days but died due to non availability of donor, and 2 underwent LT. Among those who did not complete the protocol (4 patients), one patient survived and the other 3 died on waitlist.



All those who died or received LT had HE grade 3/4 by the end point and all those who survived by 90 days were having no HE.

	0-72 hours		72-96 hours		96 hours- 90 days	
	Total (N=66)	NWI ≥ 11 (N=42)	Total (N=58)	NWI ≥ 11 (N=28)	Total (N=54)	NWI ≥ 11 (N=20)
Surviving with native liver	58	34	54	25	40	10
Death	5	5	1	1	13	9
Liver Transplant	3	3	3	2	1	1

Fig. 2 Changes in hepatic encephalopathy (HE) during hospital stay and outcome of the patients

Progression of the disease in hospital and outcome of the decompensated WD

Figure 1 depicts that 16 (47%) and 23 (71.8%) of the

children with ACLF (34) and DCLD (32) survived with native liver. Histogram in Fig. 2 shows the changes in the HE from admission to 96 h with the outcome from admission to 90 days tabulated below. As apparent from Fig. 2, there were 42 cases with NWI ≥ 11, of which 5 died and 3 got transplanted within 72 h of hospital stay. By 72 h, NWI in 11 patients improved to < 11 and hence 23 with NWI ≥ 11 were surviving at 72 h but with addition of 5 cases (whose NWI deteriorated from admission): 28 cases with NWI ≥ 11. Hence, between 72 and 96 h, 20 survived with NWI ≥ 11, 5 showed NWI < 11, 1 died and 2 got transplanted by 96 h. Between 96 h and 90 days 20 cases had NWI ≥ 11 of which 10 survived, 9 died, and 1 more got transplanted by the 35th day of admission.

Prediction of death in the decompensated WD at admission

High bilirubin (HR 1.029, 95% CI 1.007–1.052, $p = 0.008$), high INR (HR 1.73, 95% CI 1.15–2.62, $p = 0.009$), high lactate (HR 1.36, 95% CI 1.18–1.58, $p = 0.000$), NWI (HR 1.23, 95% CI 1.07–1.42, $p = 0.005$), HD score (HR 1.03, 95% CI 1.01–1.05, $p = 0.006$), PELD (HR 1.095, 95% CI 1.04–1.15, $p = 0.001$), CLIF–SOFA (HR 1.31, 95% CI 1.13–1.50, $p = 0.000$) and AARC-ACLF (HR 1.66, 95% CI 1.34–2.05, $p = 0.000$) were all significantly associated with death on univariate Cox regression analysis (Table 2). Nineteen of the 42 patients with NWI ≥ 11 survived with native liver whereas 4 of the 24 with NWI < 11 died (OR 3.28, 95% CI 1.28–8.37, $p = 0.004$). The predictive scores and the biochemical parameters could not be added to a multivariate model due to strong correlation between them. Table 3 depicts the comparative evaluation of the five predictive scores in predicting death in decompensated WD in the present cohort. As is obvious from the highest positive and lowest negative likelihood ratios as well as highest accuracy of AARC-ACLF, it is performing the best among the five predictive scores. ROC analysis of the performance of AARC-ACLF, CLIF–SOFA, and NWI as predictors for mortality at 90 days is seen in Fig. 3. The AUROC of NWI, PELD and HD score was < 0.80 whereas AARC-ACLF had the AUROC of 0.939 and the minimum standard error of 0.027 (Fig. 3). The optimal cutoff for the AARC-ACLF was found to be ≥ 11 with the sensitivity of 92% and specificity of 85% for predicting poor outcome in the decompensated WD. Table 4 shows hazard of death at 90 days predicted by the

Table 2 Univariate analysis to compare clinical and biochemical risk factors for death in decompensated Wilson disease

Variable	Death + LT ($n = 27$)	Survived with native liver ($n = 39$)	HR	95% CI	p value
HE grade 3/4	8	3	2.76	0.97–7.76	0.055
ACLF (*n*)	18	16	1.76	0.98–3.2	0.049
Ascites (*n*)	20	31	0.87	0.25–3.06	0.838
Liver atrophy (*n*)	11	11	0.949	0.38–2.39	0.912
Coomb's negative hemolysis (*n*)	19	18	2.02	0.73–5.58	0.176
Bilirubin (mg/dl)[c]	20.5 (5.15–30.5)	4 (2.1–9.2)	1.029	1.007–1.052	0.008
AST (IU/ml)[c]	181 (126–258)	120 (91–194)	1.001	1.001–1.002	0.050
INR[c]	3.4 (2.21–4)	2.54 (2.06–3)	1.73	1.15–2.62	0.009
TLC (/mm^3)[c]	10.4 (6.07–16.85)	8.9 (5.7–14.3)	1.00	1.00–1.00	0.435
Albumin (g/dl)[c]	2 (1.73–2.25)	2 (1.8–2.4)	0.817	0.34–1.96	0.651
Ammonia[c]	155 (89–212.25)	1105 (77–137)	1.003	0.99–1.008	0.316
Lactate	4.4 (3.92–5)	2.2 (2–3)	1.364	1.18–1.58	0.000
NWI[c]	14.5 (11.25–16)	10 (8–13)	1.23	1.07–1.42	0.005
HD score[c]	24.4 (8.28–34.28)	6.24 (2.6–10.33)	1.03	1.01–1.05	0.006
PELD[c]	29.5 (22–37.25)	20 (14–27)	1.095	1.04–1.15	0.001
CLIF–SOFA[c]	11 (9–13)	8 (7–10)	1.31	1.13–1.50	0.000
AARC-ACLF[c]	13 (11–14)	7 (6–10)	1.66	1.34–2.05	0.000

HR hazard ratio, *95% CI* 95% confidence interval, *HE* hepatic encephalopathy, *ACLF* acute-on-chronic liver failure, *AST* aspartate transaminase, *TLC* total leukocyte count, *INR* international normalized ratio, *HD score* score from the reference number [11], *NWI* New Wilson's Index, *PELD* Pediatric Endstage Liver Disease score, *CLIF–SOFA* chronic liver failure-sequential organ failure assessment, *AARC-ACLF* APASL ACLF Research Consortium score for ACLF

[a]HE grade 1/2 versus No HE

[b]HE grade 3/4 versus No HE and HE grade ½

[c]Median (IQR)

Table 3 Comparative evaluation of predictive scores for death at 90 days in decompensated WD

Indices	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio	Accuracy (%)
AARC-ACLF ≥ 11	92.6	84.6	6.02	0.09	87.88
NWI ≥ 11	85.19	51.28	1.75	0.29	63.64
HD score ≥ 8.2	85.71	57.89	2.04	0.25	69.7
CLIF–SOFA ≥ 9	85.19	71.79	3.02	0.21	77.27
PELD ≥ 24	77.78	61.54	2.02	0.36	68.18

WD Wilson's disease, *AARC-ACLF* APASL ACLF Research Consortium score for ACLF, *NWI* New Wilson's index, *HD score* score derived in reference no. [11], *CLIF–SOFA* chronic liver failure-sequential organ failure assessment, *PELD* Pediatric Endstage Liver Disease score

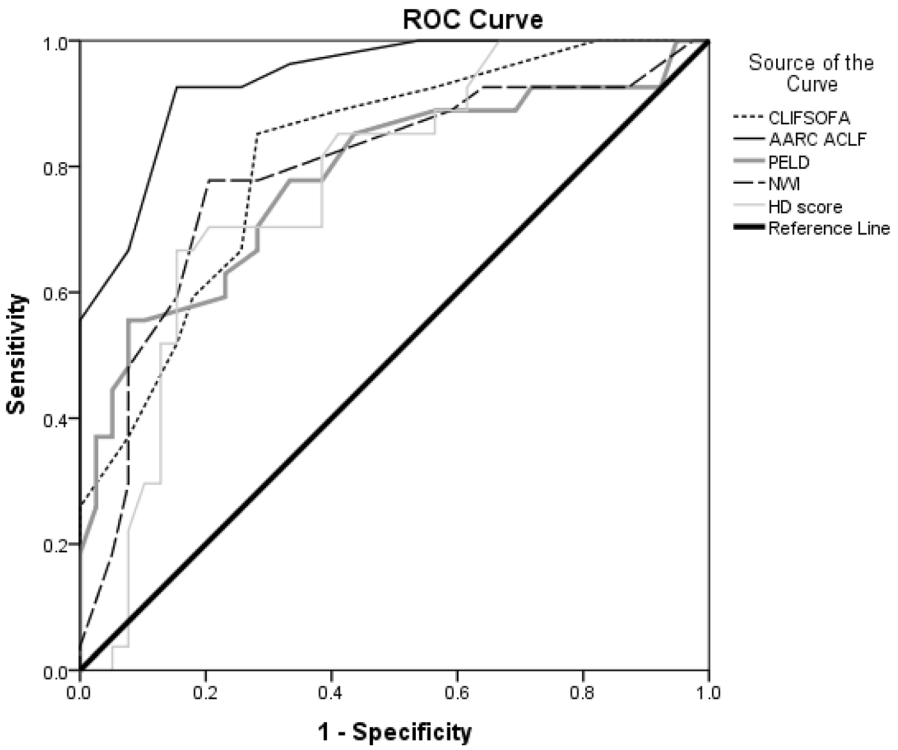


Fig. 3 ROC curves for the predictive scores to predict the mortality at 90 days in decompensated WD

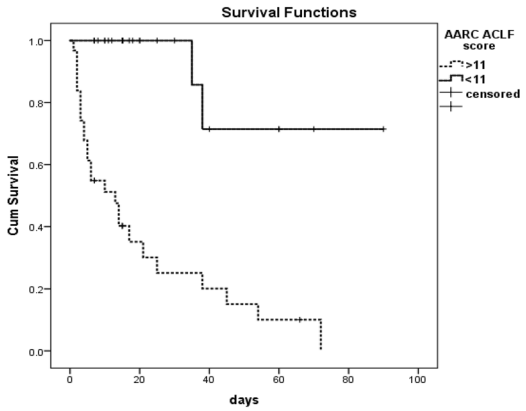
Variables	AUROC(95% CI)	Standard Error	*z statistic (p value)	**z statistic (p value)
NWI	0.789 (0.67-0.91)	0.060	2.195 (p=0.028)	NA
HD score	0.770(0.66-0.89)	0.059	4.502 (p<0.0001)	1.438(P = 0.150)
PELD	0.783 (0.66-0.90)	0.061	.239 (P = 0.025)	0.139 (P = 0.889)
CLIF SOFA	0.818 (0.72-0.92)	0.052	2.809 (p= 0.005)	0.399 (p=0.689)
AARC ACLF	0.939 (0.89-0.99)	0.027	NA	2.195 (p=0.028)

*Comparison with AARC ACLF score
*Comparison with NWI score
AARC-ACLF= APASLACLF Research Consortium. CLIF SOFA= chronic liver failure Subsequent Organ Failure Assessment score, NWI=New Wilson's index, AUROC= area under the ROC curve. ,NA=Not applicable

Table 4 Hazard of mortality at 90 days and the concordance indices for the different predictive scores

Indices	Hazard ratio (95% CI)	Harrell's C	Somer's D
AARC-ACLF	1.66 (1.21–1.75)	0.77	0.54
NWI	1.23 (1.12–1.51)	0.75	0.51
HD score	1.03 (1.01–1.05)	0.76	0.52
CLIF–SOFA	1.31 (1.13–1.49)	0.72	0.44
PELD	1.09 (1.04–1.17)	0.71	0.42

WD Wilson's disease, *AARC-ACLF* APASL ACLF Research Consortium score for ACLF, *NWI* new Wilson's index, *HD score* score derived in reference no. [11], *CLIF–SOFA* chronic liver failure-sequential organ failure assessment, *PELD* Pediatric Endstage Liver Disease score



Log Rank Test shows the Survival with AARC ACLF score of < 11 was significantly better than AARC ACLF score ≥ 11.

Fig. 4 Kaplan–Meier survival curves to see the effect of AARC-ACLF score ≥ 11 versus < 11. Log Rank Test shows the Survival with AARC-ACLF score of < 11 was significantly better than AARC-ACLF score ≥ 11

various predictive scores and their concordance. It is seen that for every unit increase of AARC-ACLF there would be 66% increase in mortality in the study cohort (HR 1.66, 95% CI 1.34–2.05). The Harell's C and Somer's D for AARC-ACLF was 0.77 and 0.54, which were the highest for the predictive scores studied. Figure 4 depicts the Kaplan–Meier survival curves of patients with AARC-ACLF ≥ 11 versus AARC-ACLF < 11. Log Rank Test shows that the survival with AARC ACLF score of < 11 was significantly better than AARC ACLF score ≥ 11.

Discussion

The present study has identified AARC-ACLF, as the best predictive score with the diagnostic accuracy of 88% to predict death in decompensated WD. Each unit increase in the AARC-ACLF score would increase mortality by 66%. The reason for the superior efficacy could be due to the similarity in the derivation cohort of the AARC-ACLF score and the cohort used in the present study where we have used the APASL definition for ACLF. The AARC-ACLF score was used previously to predict the short-term mortality and need for liver transplant in adults with ACLF [6]. AARC-ACLF has been studied in pediatric ACLF cohort and was found to be the best predictor of mortality without LT [10]. The authors found the pediatric modified scores did not add any benefit in the prediction. This is the first study to utilize the AARC-ACLF in chronically decompensated WD cohort for prediction of death at 90 days. The CLIF–SOFA score had diagnostic accuracy of 77.27% in predicting death in the decompensated WD cohort of the present study. The reason for the lower efficacy of the CLIF–SOFA score vis-a-vis the AARC-ACLF score could be due to development of the score in patients with EASL-ACLF having both hepatic and non-hepatic organ failures [11] and also that pediatric cirrhotics infrequently present with other organ failures [9, 10]. Moreover, similar to the present study, another recent Indian study [17] showed that a simple score considering only the number of organ failures is easier to recall and superior to the CLIF–SOFA score in predicting mortality in ACLF patients defined as per APASL. In the only study of its kind, pediatric CLIF–SOFA performed best in prognostication of 28-day mortality in children with DCLD with acute decompensation which was a cohort similar to the cohort used in EASL-ACLF [18].

In 2005, NWI ≥ 11 was found to be associated with death without LT [3]. In a predominantly adult series of 21 WD cases, Petrasek et al. found NWI better than the Nazer score [19]. Subsequently, doubts have been raised against this index's efficacy in predicting outcome in fulminant WD [4]. Children with NWI ≥ 11 have survived with native liver and some of those with score below 11 were eventually transplanted. In the present study also, nineteen of the 42 patients with NWI ≥ 11 survived with native liver whereas 4 of the 24 with NWI < 11 died. The study cohort in the present study was similar to the derivation cohort for NWI in the original study [3]. In a more recent study done in a non transplant centre in India, among south Indian children with WD-related ALF, HD score (2.87 × Encephalopathy + 1.07 × Total Serum Bilirubin) was found to be independently associated with poor outcome in WD [5]. The difference in the derivation cohort (being ALF) from that of the present study cohort (being ACLF and/or DCLD) should not create a bias as it is well known that almost all WD patients have cirrhosis. It is possible that non differentiation of HE into various grades in the HD score [5] is responsible for the failure of the validation of this index in the present cohort. Although in the present study HE grade 3/4 was not significantly associated with death and LT, it is possible that grades of HE and lactate could be the reason for the better

performance of the AARC-ACLF score over other scores (NWI, HD score, and PELD) as both these parameters are absent in them.

The patients with ACLF were acutely decompensated: more jaundice, coagulopathy, higher leukocyte count suggesting infections and hence, higher scores with higher short-term mortality as compared to DCLD. Mortality as high as 40% has been described in adults with ACLF [15]. On the contrary, liver atrophy was more often documented on imaging in DCLD. But in absence of acute decompensation, these children had better survival. The higher proportions (66/125, 52.8%) of decompensated WD in the present study could be due to the referral bias to a LT centre. An Indian non transplant centre reports much lower percentage of WD presenting with liver failure (26.5%) [5]. Gender distribution seen in the study is reflective of the bias in health-seeking behavior in the country. The possible reason for higher percentage (90.9%) of patients with identified KF ring in our cohort could be that the patients were older (median age was 9 years), all slit-lamp examinations were done by a single ophthalmologist and most of our patients had CLD. A previous mixed cohort of compensated and decompensated WD described presence of KF ring in 34/57 (59.6%) patients [3]. WD makes a small proportion of the ALF cohort in children, as reported earlier from US and Europe [20–22]. The same is also true for studies from India [23, 24]. Our centre has reported no WD in our ALF cohort [25] since we found evidence of CLD in them and labeled them as ACLF [6]. As is evident that the patients with ACLF at admission had more advanced liver disease and hence had higher transplant-free mortality in the subgroup (13/34 in ACLF versus 7/32 in DCLD). Proportions (54% versus 40.9%) of deaths without LT in WD with liver failure, as reported from a non transplant Indian centre [5] versus in the present study are comparable. Indian public sector transplant centre like ours is limited by logistic constrains, removal of which could potentially improve the proportions of patients receiving LT and also improve the outcome of decompensated WD in this country.

In countries like US, decompensated WD gets priority on the wait list with status 1b [26]. Initiation of chelation therapy cannot remove copper rapidly, hence even on wait list, rapid removal of free copper through HVPE can benefit patients with WD. In the present study, of the 12 children with ACLF who completed the HVPE protocol, 4 patients survived with native liver till 90 days after admission. Similarly, survival with native liver after HVPE has been reported from across the globe: in 6 of 7 Chinese children [27], 2/4 Japanese children [28], an Indian girl who died later without LT [29] and another Turkish girl child [30]. The remaining two Japanese children were successfully transplanted [28]. HVPE efficiently removes both ceruloplasmin-bound and albumin-bound copper and the fresh frozen plasma used for exchange can be helpful in treating the associated coagulopathy. As of now the recommendations are to use these modalities as bridging therapies to LT or in cases where LT is not possible. So till such time, HVPE can be a safe and effective therapy for bridging to LT in WD cases.

The limitations of this prospective study are the single centre design and screening for only five mutations and that we could not study the influence of genotype on presentation and natural history [31]. The present study is also different from rest of the studies as we used combination therapy, whether that could explain the decreased proportions of death cannot be said with certainty, although, success with combination therapy has been reported earlier [3, 32].

We conclude that AARC-ACLF score is the best predictor of mortality in decompensated WD. NWI has lower sensitivity and accuracy as a predictive tool for death in this cohort. While all patients with decompensated WD should be listed for LT, an immediate LT is indicated if AARC-ACLF ≥ 11 is present in the patient. Copper-removing therapies like HVPE have a potential role in survival with or without LT. However, there is an urgent unmet need for generation of large, multicentric pediatric ACLF data. AARC score will need validation in large multicentric pediatric ACLF cohort.

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Compliance with ethical standards

Conflict of interest Seema Alam, Bikrant Bihari Lal, Vikrant Sood, Rajeev Khanna, and Guresh Kumar declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This was a retrospective study. The study was approved by the institutional ethical review board.

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