ORIGINAL ARTICLE

Clinical Characteristics and Comparison of Different Prognostic Scores in Wilson's Disease

Zain Majid[1], Ghazi Abrar[2], Syed Mudassir Laeeq[3], Shoaib Ahmed Khan[4], Hina Ismail[5], Ghous Bux Soomro[6], Nasir Mehmood[7], Abbas Ali Tasneem[8], Farina Muhammad Hanif[9], Rajesh Mandhwani[10], Nasir Hasan Luck[11]

Abstract

Aim: Wilson's disease (WD) is a rare autosomal recessive disease, that can involve any organ of the body, the main ones being the liver and the brain. These patients can have varied presentations, ranging from having no symptoms to having neurological manifestations to features of chronic liver disease (CLD). Those patients that end up having CLD are prognosticated *via* the Child–Turcotte–Pugh (CTP) score and the Model for End-stage Liver Disease (MELD) score. However, two specific scores exist for prognostication in patients having WD, namely, the Nazar score and the Dhawan score. However, these are yet to be validated nor has their use been implemented in clinical practice.

Materials and methods: Our study involved 65 patients with WD, comprising both the pediatric and the adult population. We aimed at evaluating the clinical manifestations the lab parameters and the management of these patients. Furthermore, we tried validating the Nazar and the Dhawan score and later compared them with the CTP and the MELD score, which are well-known prognostic tools in CLD.

Results: Our patients were subdivided into the pediatric (more than 50%) and the adult group. The most common presenting complaint noted in both groups was abdominal distension. Values of the urine copper and serum ceruloplasmin did not defer between the pediatric and adult patients. Hepatic involvement is frequently seen in the pediatric age-group. Also, CTP class C was chiefly seen in pediatrics 17/33 (51.5%), while CTP class B was in adults 13/32 (40.6%). The mean Nazar score was 3 ± 3, while the mean Dhawan score was 5 ± 4. The main treatment offered for both groups was zinc along with penicillamine.

Conclusion: Our study showed the Dhawan score was comparable to the CTP and the MELD score in terms of predicting the disease severity of WD in our patient population.

Keywords: Child–Turcotte–Pugh score, Dhawan score, Hepatic disease, Kayser-Fleischer rings, Model for End-stage Liver Disease Score, Nazar score, Neurological symptoms, Pakistan, Wilson's disease.

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Introduction

Wilson's disease, alias hepato–lenticular degeneration, is an uncommon autosomal recessive disease that leads to the excess copper accumulation in the body namely in the liver, the basal ganglia, the cornea, and other organs.[1]

First recognized by Kinner Wilson in 1912,[2] It occurs due to a mutation in the copper-carrying ATPase (ATP 7B) gene, the genetic defect of which is localized to the long arm of chromosome 13 that modifies ATP 7B gene in the liver. Since copper is mainly expelled *via* the liver, this excess copper is accumulated and then spills over into the blood, which in turn generates free radicals that oxidize proteins and lipids in the body.[1]

We, through this study, shared our data on patients having WD, their clinical manifestations along with treatment options.

Materials and Methods

This cohort study was conducted retrospectively (by reviewing the medical records) at the Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan from January 2015 to December 2021. The department of Hepatogastroenterology, SIUT is one of the largest hepato–biliary units in the country and receives patients from all over the country. All patients who were newly diagnosed as having WD as per the criteria laid down by the American Association for the Study of Liver Diseases (AASLD) of either gender, aged 2 years and above; visiting the gastrointestinal (GI) clinic or admitted *via* emergency were included in this study. Informed written consent was obtained from the patient or guardian prior to their inclusion. This study was approved by the ethical review board of our hospital.

Various laboratory parameters were checked including complete blood count (CBC), urea creatinine and electrolytes (UCEs); liver function tests (LFTs); albumin; prothrombin time and international normalized ratio (PT/INR); and other serological workup was done to rule out competing etiologies including viral serology [HBsAg, anti-hepatitis C virus (HCV)], autoimmune profile [antinuclear antibody test (ANA), antimitochondrial antibodies (AMA), anti-smooth muscle antibodies (ASMA), anti–liver-kidney microsomal antibody (anti-LKM)].

An ultrasound abdomen was performed to rule out the presence of features of CLD. Upper GI endoscopy was done to rule

[1–11]Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan

Corresponding Author: Zain Majid, Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan, Phone: +923333171160, e-mail: zain88@hotmail.com

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out varices. Slit lamp examination was done for the presence of Kayser-Fleischer (KF) rings by an experienced ophthalmologist.

Later the CTP score and the MELD score were calculated to assess severity of liver disease. Nazar et al. and the Dhawan score were calculated and compared with CTP and MELD score; $p \leq 0.05$ was taken as statistically significant.

All the data were entered and analyzed using Statistical Package for the Social Sciences (SPSS), version 24.0.

For categorical variables such as gender, comorbid conditions, etiology of cirrhosis, CTP score (severity of liver disease), and comorbid, frequency and percentage were calculated. For continuous variables such as age, ceruloplasmin, 24-hour urine copper, etc., the mean and standard deviation (SD) were determined.

Later on, the Chi-squared test was used for the correlation analysis between the CTP, MELD score, Nazar score, and Dhawan score.

Results

A total of 65 patients were included in this study, with males being the predominantly gender noted in 41/65 (63.1%) patients. The mean age noted was 15 ± 7.4 years. Our patients were subdivided between the pediatric (those aged less than 15 years) and the adult group. Age less than 15 years was noted in 33/65 (50.8%) patients, while age more than 15 years was seen in 32/65 (49.2%) individuals (baseline laboratory parameters are shown in Table 1).

Table 1: Baseline lab parameters of patients with WD

	Minimum	*Maximum*	*Mean*	*SD*
CTP	5.00	19.00	8.9194	3.069
MELD	5.00	35.00	15.8367	7.962
Ceruloplasmin (mg/dL)	2.00	60.00	13.4430	11.028
Urine_CU (µg)	0	1050	230.34	244.070
Hemoglobin (gm/dL)	5.70	15.90	10.4815	2.242
TLC cells/mm^3	0.70	27.00	7.4057	4.901
Platelets (×10^9/L)	28.00	706.00	142.2500	135.767
INR	0.00	6.10	1.8048	1.032
Urea (mg/dL)	0.00	80.00	22.2241	13.071
Cr (mg/dL)	0.09	1.49	0.5413	0.245
Na (meq/L)	120.00	410.00	140.5161	35.259
K (meq/L)	2.70	34.00	4.4097	3.869
Cl (meq/L)	88.00	136.00	105.9194	7.037
HCO_3 (meq/L)	12.00	30.00	21.2667	3.517
TBR (mg/dL)	0.33	38.80	4.9397	7.782
DBR (mg/dL)	0.03	20.40	2.2804	4.158
ALP (U/L)	35.00	980.00	267.4754	167.443
SGOT (U/L)	0	292	101.45	71.059
SGPT (U/L)	13	331	76.86	68.427
GGT (U/L)	0	282	78.44	76.842
Albumin (gm/dL)	1.28	4.90	2.8217	0.857

ALP, alkaline phosphatase; CTP, child–turcotte–pugh; DBR, direct bilirubin; GGT, gamma-glutamyl transferase; MELD, model for end-stage liver disease; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TBR, total bilirubin; TLC, total leukocyte count

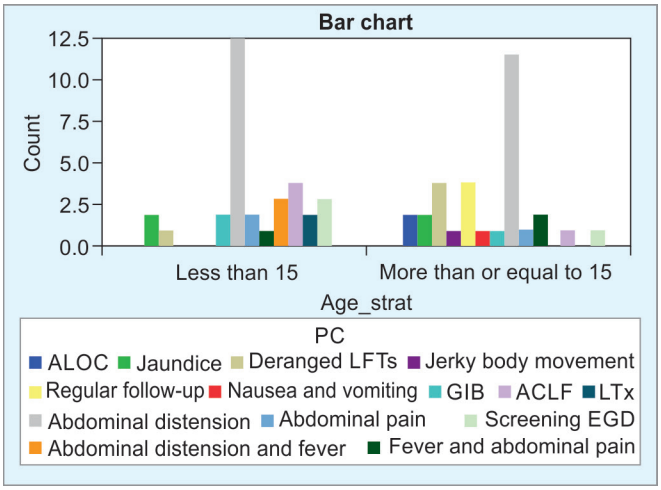

Fig. 1: Age-wise distribution of the presenting complaints

The most common presenting complaint appreciated in our patients was abdominal distention, seen in 25/65 patients (38.5%), 5/65 (7.7%) patients were admitted with the impression of acute on chronic liver failure (ACLF), while 4/65 (6.2%) had presented with either jaundice or deranged LFTs. Fever and abdominal pain were noted in 3/65 (4.6%) patients. The most common presenting complaint seen in both the pediatric and the adult patients was abdominal distension, noted in 13/33 (39.3%) pediatrics cases, while 12/32 (37.5%) in adults (Fig. 1). The patients were later subdivided into those having liver involvement 52/65 (80%), liver along with neurological involvement in 4/65 (6.1%), those with neurological involvement only in 3 (4.6%) and those who were asymptomatic seen in 6 cases (9.2%) (Table 2).

Values recorded for the mean serum ceruloplasmin were 13.4 ± 11 mg/dL and the mean 24-hour urinary copper was 230 ± 248 µg. Values of the urine copper and serum ceruloplasmin did not defer between the pediatric and adult patients ($p = 0.438$). Kayser-Fleischer rings were evident in 28/65 (43.1%). While ANA was positive in 8/65 (12.3%) patients only, the viral markers (HbsAg and anti-HCV) were negative in the majority of our patients 62/65 (95%). The mean CTP score and the mean MELD scores were B9 and 16, respectively. Being in a particular CTP class did not correlate with the values of serum ceruloplasmin and 24-hours urine copper excretion ($p = 0.48$).

Features attributed to CLD on ultrasound abdomen were noted in 46/65 (71%) cases. Esophageal varices were evident in 16/65 (24.6%) patients with WD. Liver parenchymal biopsy was performed in 4/65 cases (6%), which was mainly done due to suspicion of overlapping pathology. One of these biopsy specimens had shown features suggestive of autoimmune hepatitis (AIH) (piecemeal necrosis along with plasma cells and portal inflammation); however, the diagnosis of WD was further confirmed after obtaining 24-hour urinary copper results. The ceruloplasmin levels did not differ between the pediatric and the adults. A magnetic resonance imaging (MRI) brain was done in 6/65 cases (9%), the findings of all of which showed hyperintense signals in the basal ganglia.

Hepatic involvement which is frequently seen in the pediatric age-group, was noted in 30/33 children (90.9%) as compared to adults 20/33 (60.6%) while neurological involvement was noted more in the adult group 3/32 (9.4%) vs none in the pediatric group ($p = 0.011$). Hepatic along with neurological manifestations were noted more in the pediatric group 3/33 (9.1%) as compared to the

Table 2: Presenting complaint distribution according to the pediatric and adult age-groups

	Presenting complaint subdivision				
	Hepatic	*Neurological*	*Asymptomatic*	*Hepatic and neurological*	*Total*
<15 (Pediatric)	30	0	0	3	33
≥15 (Adults)	22	3	6	1	32
Total	52	3	6	4	65

Table 3: Age-wise distribution of the CTP class

	CTP class			
Age-wise stratification	*A*	*B*	*C*	*Total*
Less than 15	7	10	16	33
More than or equal to 15	11	13	8	32
Total	18	23	24	65

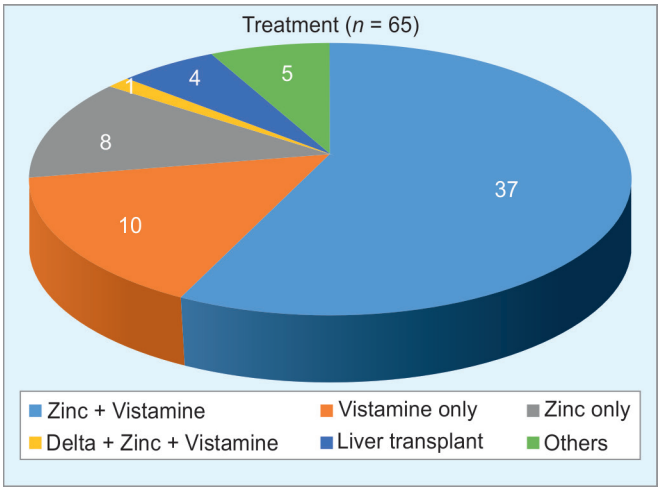

Fig. 2: Different treatments offered to patients with WD at our hospital

adult group 1/32 (3.1%). Kayser-Fleischer rings were noted more in the adults group 16/32 (50%). The CTP class C was chiefly seen in pediatrics 17/33 (51.5 %), while CTP class B was seen in adults 13/32 (40.6%) (shown in Table 3). Even though the pediatric age-group had more patients who were diagnosed with features of CLD as compared to the adult group but with a $p \leq 0.097$, which was not statistically significant.

The combination of zinc with D-penicillamine was the most common treatment offered in 37/65 (56.9%) cases followed by D-penicillamine alone in 10/65 (15.3%) and by zinc alone in 8/65 (12.3%). One patient had been on steroids with zinc and D-penicillamine due to the suspicion of WD along with AIH (Fig. 2).

The mean Nazar score was 3 ± 3, while the mean Dhawan score 5 ± 4. A Nazar score more than or equal to 7 was noted in 9/65 (13.8%) while Dhawan score of more than or equal to 11 in 9/65 (13.8%). Most of our patients with WD were alive and on regular follow-up, 58/65 (89.2%).While live-related liver transplant was done in 4/65 (6%) cases and 2 of our patients did not follow back to us, 3 patients had passed away.

When a Nazar score of 7 and above was used, it did not correlate with the CTP score ($p \leq 0.083$) but was related to the MELD ($p \leq 0.025$).

While a Dhawan score of 11 and above, correlated both with the CTP score ($p \leq 0.02$) along with the MELD score ($p \leq 0.025$). A Nazar score of 7 or more was seen more in the pediatric group (7 pediatric vs 2 adults) but with a non-significant p-value (0.081). While a Dhawan score of 11 and above was noted more in the pediatric age-group 8 vs 1 in the adult ($p \leq 0.014$) which was likely due to the delay in diagnosis leading to the occurrence of liver disease in the pediatric age-group.

Discussion

The World Health Organization (WHO) estimates the global prevalence of WD to be around 1/10,000 to 1/30,000.[2] Its prevalence in Europe is ranging from 1.2 to 2/100,000 but a higher genetic prevalence of 1/7,000 is noted in these regions.[3] The highest rates of WD are seen in some parts of Europe, namely, in countries such as Romania and Sardina.[4]

Liver dysfunction is usually evident by the first decade, while neurological symptoms are apparent in the third and fourth decades of life.[1]

The age spectrum for presentation for WD is wide, with cases of WD being reported in patients as young as 3 years of age and a few noted in people in the eighth decade of life.[5]

The Indian Guideline on WD noted the frequency of seeing patients diagnosed with WD to be around 7.6–19.7% in tertiary care centers.[4] There is a paucity of data on WD from Pakistan with the clinical prevalence of the disease still largely unknown in Pakistan.[6] A prior study done in Multan, Pakistan involving over 14,000 children found the prevalence of WD to be 0.33% in children up to the age of 16 years.[7]

Parkash et al., in a retrospective study demonstrated the clinical manifestations along with the laboratory parameter of patients with WD presenting at a large tertiary care center in Karachi, Pakistan.[6]

Clinical symptoms of the disease are broadly divided into hepatic, neurological, and psychiatric; with liver disease being the first manifestation in 60% of patients having WD.[8] However, the involvement of any organ of the body can occur due to copper accumulation.[8]

Liver manifestation range from asymptomatic to acute hepatitis to acute liver failure (ALF) and CLD.[8]

Neurological manifestations are the second predominant complaints, which are seen in 18–68% of those having WD, having a mean age of onset of 20–30 years.[8]

Ophthalmic manifestation of the disease includes KF rings and sunflower cataract. Kayser-Fleischer ring are noted in almost all patients diagnosed with neurological WD, in 40% of hepatic WD and in 20% of pre-symptomatic people diagnosed with WD.[9]

Mood disturbance are the most common psychiatric symptoms seen in WD, with depression seen in 20–60% of the cases.[9]

The diagnosis of WD is made based on 2 out 3 of the following as per the AASLD recommendations, namely, serum ceruloplasmin less than 20 mg/dL (an even lower serum ceruloplasmin level less than 5 mg/dL is taken as a strong evidence of the disease); urinary copper excretion values of more than 100 µg in 24 hours and or the presence of KF rings.[10]

A liver biopsy is rarely required for the diagnosis, but maybe used to rule out other conditions.[10] While MRI brain is needed when neurological involvement is suspected, with the T2-weighted image showing hyperintense signals in the basal ganglia.[11]

The CTP score and MELD are well-known prognostic scores that predict disease severity and mortality in decompensated liver disease regardless of the etiology.[12] The Nazar et al. and the Dhawan score are two prognostic scores used specifically in patients having WD who present with signs of decompensation.[13]

The Nazar score, first published in 1986, was later validated, improved, and later on, led to creation of the Dhawan score in 2005. However, both the scores are yet to be authenticated in large clinical studies.[13]

The Nazar score has three components, namely, the total bilirubin (TBR), aspartate aminotransferase (AST), and INR. A score of greater than or equal to 7 predicts death without liver transplantation.[13] While the Dhawan score comprises of the five components, namely, TBR, AST, INR, white blood cell (WBC), and albumin, a score of greater than equal to 10 predicts death without liver transplant.[13]

Wilson's disease, is a recognized genetic disorder which is treatable.[4] Treatment for WD has two main options, namely, pharmacological therapy (taken lifelong) and liver transplantation for those presenting with end-stage liver disease or ALF.[14]

The pharmacologically therapy involves the use of chelating agents. Most patients have an improvement noted 18 months post therapy.[4] Copper chelation agents are mainly used for treatment of WD and includes penicillamine, trientine, tetrathiomolybdate, and zinc. While liver transplant is only indicated in selective cases (end-stage liver disease due to WD) and in the case of ALF due to WD.[10]

Moreover, D-penicillamine is the drug of choice used in WD.[4] It may cause deterioration in symptoms while treating neurological Wilson, hence other options are recommended.

Many clinicians prefer trientine, which has fewer side effects;[10] however, this drug is still unavailable in Pakistan. A case series form India recommended the combination of trientine and zinc for the initial treatment of ALF due to WD.[15]

For neuromuscular symptoms, such a rigidity, spascity baclofen, gaba antagonist, or levodopa are used, which is usually aided by physiotherapy and exercise.[4] Liver transplant is the main treatment for end-stage liver disease due to WD but it is usually not opted for in the presence of neuropsychiatric symptoms.[16] An Italian cohort reported excellent patient and graft survival after LTx in WD with 1 year graft survival of 92%.[16] However, their study showed that neurological symptoms had resolved in only a few cases.[16]

Poor outcome for neurological WD is seen in those with severe brain changes noted on MRI brain and in people having a strong family history.[17]

Conclusion

This is one of the first few studies from Asia that compared the different prognostic scores in patients with WD and showed that the Dhawan score was comparable to both the CTP and the MELD score in terms of prognostication for the severity of liver disease. Further studies are needed to validate these scores in these patients. A limitation of our study was that survival analysis was not calculated; however, since these patients are currently on regular follow-up, further data will be collected in this regard.

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