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Editorial Board Member of *World Journal of Clinical Cases*, Nicola Montemurro, MD, PhD, Assistant Professor, Consultant Physician-Scientist, Neurosurgeon, Surgeon, Surgical Oncologist, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa 56126, Italy. nicola.montemurro@unipi.it

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Retrospective Study

Pediatric Wilson disease presenting as acute liver failure: Prognostic indices

Wei-Yuan Fang, Kuerbanjiang Abuduxikuer, Peng Shi, Yi-Ling Qiu, Jing Zhao, Yu-Chuan Li, Xue-Yuan Zhang, Neng-Li Wang, Xin-Bao Xie, Yi Lu, A S Knisely, Jian-She Wang

ORCID number: Wei-Yuan Fang 0000-0003-3619-2414; Kuerbanjiang Abuduxikuer 0000-0003-0298-3269; Peng Shi 0000-0002-0626-4555; Yi-Ling Qiu 0000-0002-7296-9115; Jing Zhao 0000-0002-3208-9009; Yu-Chuan Li 0000-0003-1769-3459; Xue-Yuan Zhang 0000-0003-4258-1731; Neng-Li Wang 0000-0001-6967-9873; Xin-Bao Xie 0000-0002-3692-7356; Yi Lu 0000-0002-3311-4501; A S Knisely 0000-0002-9173-539X; Jian-She Wang 0000-0003-0823-586X.

Author contributions: Fang WY and Abuduxikuer K contributed equally to this work and were in charge of data acquisition, analysis, interpretation, and writing; Wang JS and Lu Y contributed to the study design and critical revision; Abuduxikuer K, Shi P, and Qiu YL contributed to the statistical analyses; Knisely AS contributed to the manuscript review; Zhao J, Li YC, Zhang XY, Wang NL, and Xie XB contributed to the patient's medical management; All authors have read and approved the final manuscript.

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Wei-Yuan Fang, Kuerbanjiang Abuduxikuer, Yi-Ling Qiu, Jing Zhao, Yu-Chuan Li, Xue-Yuan Zhang, Neng-Li Wang, Xin-Bao Xie, Yi Lu, Jian-She Wang, Center for Pediatric Liver Diseases, Children's Hospital of Fudan University, Shanghai 201102, China

Peng Shi, Medical Statistics Department, Children's Hospital of Fudan University, Shanghai 201102, China

A S Knisely, Institut für Pathologie, Medizinische Universität Graz, Graz 8010, Austria

Corresponding author: Yi Lu, MD, Associate Chief Physician, Center for Pediatric Liver Diseases, Children's Hospital of Fudan University, No. 399 Wanyuan Road, Shanghai 201102, China. luyi@fudan.edu.cn

Abstract**BACKGROUND**

Acute liver failure (ALF) can be a primary presentation of Wilson disease (WD). Mortality rates are high in WD with ALF (WDALF). Predictions of mortality in WDALF vary by model and are sometimes contradictory, perhaps because few patients are studied or WD diagnoses are questionable.

AIM

To determine the outcomes among well-documented WDALF patients and assess mortality model performance in this cohort.

METHODS

We reviewed the medical records of our pediatric WDALF patients ($n = 41$ over 6-years-old, single-center retrospective study) and compared seven prognostic models (King's College Hospital Criteria, model for end-stage liver disease/pediatric end-stage liver disease scoring systems, Liver Injury Unit [LIU] using prothrombin time [PT] or international normalized ratio [INR], admission LIU using PT or INR, and Devarbhavi model) with one another.

RESULTS

Among the 41 Han Chinese patients with ALF, WD was established by demonstrating *ATP7B* variants in 36. In 5 others, Kayser-Fleischer rings and Coombs-negative hemolytic anemia permitted diagnosis. Three died during hospitalization and three underwent liver transplantation (LT) within 1 mo of

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presentation and survived (7.3% each); 35 (85.4%) survived without LT when given enteral D-penicillamine and zinc-salt therapy with or without urgent plasmapheresis. Parameters significantly correlated with mortality included encephalopathy, coagulopathy, and gamma-glutamyl transpeptidase activity, bilirubin, ammonia, and serum sodium levels. Area under the receiver operating curves varied among seven prognostic models from 0.981 to 0.748 with positive predictive values from 0.214 to 0.429.

CONCLUSION

WDALF children can survive and recover without LT when given D-penicillamine and Zn with or without plasmapheresis, even after enlisting for LT.

Key Words: Acute liver failure; *ATP7B*; D-penicillamine; Liver transplant; Wilson disease; Zinc

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Core Tip: This study determined outcomes among 41 recently seen pediatric patients with well-documented Wilson disease (WD) with acute liver failure (ALF) (WDALF) (most confirmed genetically, WD presenting as ALF) and assessed mortality model performances. Mortality was low, showing that WDALF children, including those with milder encephalopathy, can survive and recover without liver transplant (LT) when given D-penicillamine and zinc-salt therapy with or without plasmapheresis. Sensitivity of seven different prognostic scoring systems was good in our patients but without optimal positive predictive values, indicating that pediatric WD with higher prognostic scores may recover from ALF even after enlisting for LT.

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INTRODUCTION

Wilson disease (WD) is an autosomal recessively inherited monogenic copper toxicosis caused by mutation in *ATP7B*, which encodes a copper transporter. The worldwide prevalence of WD is 1/10000-1/30000[1,2]; its prevalence in China is unknown. WD is diagnosed principally in children and young adults[3].

Clinical manifestations of WD vary. Primary are liver disease, neuropsychiatric disturbances, Kayser-Fleischer (K-F) rings, and acute episodes of Coombs-negative hemolysis with or without anemia. Liver disease ranges from biomarker abnormalities only to acute liver failure (ALF). From 9% to 63.8% of WD may initially present as ALF[4-7]. Patients with WD with ALF (WDALF) have long-standing liver disease, including cirrhosis.

Many untreated WDALF patients die (up to 95%)[8]. Liver transplantation (LT) is advocated in WDALF because medical therapy is seen as ineffective, and WDALF constitutes 6%-12% of all ALF referred for emergent LT[9]. However, as some patients with WDALF do survive without LT[6,7,10-13], the need for LT in WDALF is not absolute.

Prognostic scoring systems are credited with identifying which liver-disease patients are at high risk of death without LT. Specific systems for WD include the Nazer score[7], King's College Hospital Criteria (KCHC; revised from Nazer score)[7], and the Devarbhavi model[6]. Other systems for predicting mortality or assisting in LT allocation for liver disease of any etiology include the Liver Injury Unit (LIU) and admission LIU (aLIU) scoring systems[14,15] and model for end-stage liver disease/pediatric end-stage liver disease (MELD/PELD) scoring systems[16]. A new prognostic score (pediatric ALF-Delta score [PALF-Ds]) to predict mortality in PALF has recently emphasized day-to-day changes in total bilirubin (TB) and international

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normalized ratio (INR) as useful in prediction[17].

Evaluations of different scoring systems in WD or WDALF have reached varying or even contradictory conclusions[12]. Reports of small numbers of patients from individual centers[5,12] or of adult patients[10] did not assist in prognostic model validation for children. In the largest cohort of pediatric WDALF ($n = 61$) in which scoring systems were assessed[6], WD was diagnosed when a score of ≥ 4 was assigned, as developed by the 8th International Conference on Wilson's Disease and Menke's Disease in Leipzig[2,9,18,19] ("Leipzig score"; range, 0–16) and calculated by including serum ceruloplasmin (Cp) and 24-h urine copper values. Such testing may, however, be less reliable in WDALF than in stable WD[20]. Of note is that to date, correlations between scoring system results and outcome have not been reported in pediatric WDALF cohorts in whose members the diagnosis of WD is genetically established.

We present the results of a retrospective analysis of 41 WDALF patients from a single pediatric liver center, 36 with documented *ATP7B* variants, and of comparison and validation of several mortality prognosis scoring systems in the 41-member cohort.

MATERIALS AND METHODS

Patients

In this retrospective study, we investigated the demographics, clinical characteristics, laboratory test results, treatments, and outcomes (with follow-up) of WDALF patients who visited the Children's Hospital of Fudan University (Shanghai, China) from January 2013 to May 2019.

ALF in children and adolescents (age < 18) was defined as acute onset of symptoms accompanied by liver-derived coagulopathy (prothrombin time [PT] ≥ 20 s or international normalized ratio [INR] ≥ 2.0 uncorrectable by parenteral administration of vitamin K in absence of encephalopathy, or PT ≥ 15 s or INR ≥ 1.5 in the presence of encephalopathy) within 8 wks of clinical onset of liver injury and without known pre-existing liver disease, according to PALF study group criteria[13,21,22]. Among the ALF children, 36 patients with 2 or more *ATP7B* variants (disease-causing or predicted disease-causing) and 5 with a K-F ring and Coombs-negative hemolytic anemia (CNHA) were considered WDALF. All WDALF patients had Leipzig scores of ≥ 4 (Supplementary Table 1).

Hematological and biochemical studies included determinations of biomarkers for hepatobiliary and renal injury or functional impairment together with Cp (assessed by immunonephelometry), 24 h urinary copper (assessed by atomic absorption spectrophotometry), PT/INR values and active partial thromboplastin times, complete blood counts with reticulocyte counts (shown as ratio of reticulocyte to erythrocyte count), and Coombs testing. Ultrasonography of the abdomen and magnetic resonance imaging (MRI) of the brain were also performed. Alternative causes of ALF such as viral hepatitis A, B, C, D and E, cytomegalovirus and Epstein-Barr virus infection, autoimmune hepatitis, and other entities were excluded by appropriate tests. Slit-lamp ophthalmoscopy was used to determine if K-F rings were present.

ATP7B analysis was done by targeted Sanger sequencing or next-generation genetic sequencing of DNA extracted from peripheral white blood cells in the Molecular Genetic Diagnosis Center, Children's Hospital of Fudan University (Shanghai, China) or at MyGenostics (Beijing, China), as previously described[23]. When two or more *ATP7B* variants were detected, confirmation of parental origins was suggested. Among the 41 patients, 36 underwent gene sequencing; five families declined on behalf of the proband. Among the 72 parents approached, 20 (parents of 10 patients) agreed to undergo sequencing and 52 parents declined. All parents self-identified as Han Chinese. All *ATP7B* variants were categorized as either severe or non-severe without reference to clinical manifestations of disease[24]. Frameshift, nonsense, and canonical splicing mutations were defined as severe; and missense mutations described in association with WD and novel missense variants predicted to be damaging were considered non-severe.

ALF children were managed supportively in our intensive care center. All interventions were undertaken only with informed parental consent. Patients received intravenous dextrose infusions and, if infection was suspected, intravenous antibiotics.

Once WDALF was suspected, plasma exchange (PE) was suggested to the patients with hepatic encephalopathy, with hyperammonemia, or with obvious hemolytic anemia and progressively and substantially increased bilirubin at the same time when

other measures (lactose, arginine, *etc.*) were carried out. Continuous hemodiafiltration was considered when renal insufficiency or hyperammonemia was present. Patients with progressive deterioration (KCHC ≥ 11) were listed for LT. Other supportive treatment (*e.g.*, intubation, mechanical ventilation) was provided as clinically required. WD-specific treatment began immediately with zinc (Zn) salt given orally or enterally. D-penicillamine was given in a small initial dose (generally 5 mg/kg or less, twice daily) to patients without progressive deterioration when WD was strongly suspected. The dose was increased gradually under close monitoring (maximum, 10-20 mg/kg/d). Outcome was defined as death without LT, survival with LT, and survival without LT. Both death and LT were considered poor outcomes. Follow-up for survivors with and without LT was obtained during outpatient visits or by telephone interview.

Supplementary Table 2 presents a summary of the different scoring systems employed (KCHC, MELD [MELD-Na]/PELD, LIU-PT, LIU-INR, aLIU-PT, aLIU-INR, Defarbhavi model, and PALF-Ds), with parameters taken into account, algorithms used for calculation of scores, and treatments indicated by scores assigned.

Statistical analysis

Statistical analyses were performed with SPSS software version 23.0 (IBM SPSS, Chicago, IL, United States). Continuous variables were presented and summarized as means \pm SD and categorical variables were summarized as frequency or percentages. As a measure of accuracy in predicting mortality, receiver operating curves, areas under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for all scoring systems. Unpaired Student's *t*-test (for variables with normal distribution) or Mann-Whitney *U* test (for variables not normally distributed) were used to compare continuous variables. Pearson chi-square testing was used for categorical variables. Fisher's exact values were calculated when expected frequency was < 5 . Two-sided $P < 0.05$ was considered statistically significant. The statistical methods of this study were reviewed by Peng Shi (Medical Statistics Department, Children's Hospital of Fudan University), and Kuerbanjiang Abuduxikuer (MPH, The Center for Pediatric Liver Diseases, Children's Hospital of Fudan University).

RESULTS

Presenting clinical features and laboratory findings of WDALF patients

From January 2013 to May 2019, 41 pediatric patients were diagnosed with WDALF in our Liver Center. Thirty-six (36/41, 87.8%) harbored two or more variants from *ATP7B* consensus sequence (**Table 1** and **Supplementary Table 3**) and were considered to have WD. Among the five patients (5/41, 12.2%) in whom *ATP7B* was not sequenced, all had K-F rings and CNHA at onset of ALF; thus they were also considered to have WD with Leipzig scores ≥ 4 . Ratios of ALP/TB (ALP IU/L, TB mg/dL; 99.00 ± 146.30 , range 0.52-734.01) ranged widely, and were < 4 in only 8 patients (8/41, 19.5%). Aspartate transaminase (AST)/alanine aminotransferase (ALT) ratios varied (2.87 \pm 2.56, range 0.58-13.88) and were > 2.2 in 15 patients (15/41, 36%). In 18 patients (18/41, 43.9%) ALP/TB < 4 or AST/ALT > 2.2 were observed (**Supplementary Table 1**).

The median age of our 41 WDALF patients at admission and diagnosis was 10.43 \pm 2.56-years-old (range, 5.61-15.25-years-old). Males ($n = 22$) slightly outnumbered females ($n = 19$). All WDALF patients had diverse non-specific and hepatic-disease-related signs and symptoms such as vomiting, abdominal pain, and hepatomegaly. Disease in 39% (16/41, 39%) had neurologic features (encephalopathy, limb numbness, headaches, and tremor) (**Supplementary Table 4**). Only 7 of 41 (17.1%) had encephalopathy when admitted to our hospital, ranging between Grade I and Grade II. Thirty-six (36/41, 87.8%) patients had K-F rings.

All had low serum Cp concentrations (0.07 ± 0.03 g/L); in 38 (38/41, 92.7%) Cp was < 0.1 g/L. All patients in whom urinary copper was measured ($n = 39$) had elevated values (2133 ± 1940 $\mu\text{g}/24$ h); in 2 patients, time constraints precluded study. Twenty-one of forty-one (51.2%) had CNHA. Thirteen patients had bilirubin values > 171 $\mu\text{mol}/\text{L}$ at admission, and in three others, bilirubin values rose over 171 $\mu\text{mol}/\text{L}$ after admission. **Table 2** shows other biomarker values in the patients.

Treatments and outcomes

In these 41 WDALF patients, 35 survived without LT (follow-up 44.6 \pm 21.9 mo), 3 died within 15 d after admission, and 3 received LT within 1 mo after admission. In all, 11

Table 1 Results of *ATP7B* sequencing in patients with Wilson disease with acute liver failure

Patient No.	<i>ATP7B</i> variants		Category of variants	Outcome
1	c.314C>A, p.Ser105X ²	c.3700delG, p.Val1234Leufs*96 ²	Biallelic severe	Liver transplant
2	c.2333G>T, p.Arg778Leu/c.2310C>G, p.Leu770Leu ¹	c.3517G>A, p.Glu1173Lys	Non-severe	Liver transplant
3	c.2333G>T, p.Arg778Leu/c.2310C>G, p.Leu770Leu ¹	c.3089Gly>A, p.Gly1030Asp ³	Non-severe	Survival
4	c.2975C>T, p.Pro992Leu	c.2975C>T, p.Pro992Leu	Non-severe	Survival
5	c.994G>T, p.Glu332X	c.1529T>C, p.Leu510Pro ³	Monoallelic severe	Survival
6	c.2455C>T, p.Gln819X ³	c.1842_1845delins23 ³	Biallelic severe	Survival
7	c.2975C>T, p.Pro992Leu	c.2975C>T, p.Pro992Leu	Non-severe	Survival
8	c.994G>T, p.Glu332X	c.994G>T, p.Glu332X	Biallelic severe	Survival
9	c.2621C>T, p.Ala874Val/c.4072delG, p.Ala1358Profs*35 ^{1,2}	c.2975C>T, p.Pro992Leu ²	Monoallelic severe	Death
11	c.2333G>T, p.Arg778Leu	c.3182G>A, p.Gly1061Glu	Non-severe	Survival
12	c.2333G>T, p.Arg778Leu	c.2621C>T, p.Ala874Val	Non-severe	Death
13	c.2975C>T, p.Pro992Leu ²	c.3443T>C, p.Ile1148Thr ²	Non-severe	Survival
14	c.2333G>T, p.Arg778Leu/c.2310C>G, p.Leu770Leu	c.1708-5T>G,	Monoallelic severe	Survival
15	c.3517G>A, p.Glu1173Lys	c.3884C>T, p.Ala1295Val	Non-severe	Liver transplant
16	c.2356-2A>G	c.2333G>T, p.Arg778Leu/c.2310C>G, p.Leu770Leu ¹	Monoallelic severe	Survival
17	c.2333G>T, p.Arg778Leu/c.2310C>G, p.Leu770Leu ¹	c.2975C>T, p.Pro992Leu	Non-severe	Survival
18	c.2333G>T, p.Arg778Leu/c.2310C>G, p.Leu770Leu ¹	c.3809A>G, p.Asn1207Ser	Non-severe	Survival
21	c.2932_2933insG, p.Val978Glyfs*50 ^{2,3}	c.2333G>T, p.Arg778Leu ²	Monoallelic severe	Survival
22	c.1708-1G>C	c.2333G>T, p.Arg778Leu	Monoallelic severe	Survival
23	c.1708-1G>C	c.2333G>T, p.Arg778Leu	Monoallelic severe	Survival
24	c.2528G>A, p.Gly843Glu ³	c.2975C>T, p.Pro992Leu	Non-severe	Survival
25	c.2975C>T, p.Pro992Leu	c.2975C>T, p.Pro992Leu	Non-severe	Survival
26	c.2543dupG, p.Asn849Glnfs*5 ^{2,3}	c.2924C>A, p.Ser975Tyr ²	Monoallelic severe	Survival
27	c.2333G>T, p.Arg778Leu	c.2975C>T, p.Pro992Leu	Non-severe	Survival
28	c.2975C>T, p.Pro992Leu	c.2668G>A, p.Val890Met	Non-severe	Survival
29	c.2924C>A, p.Ser975Tyr	c.2128G>A, p.Gly710Ser	Non-severe	Survival
30	c.2620G>C, p.Ala847Pro ²	c.2621C>T, p.Ala874Val ²	Non-severe	Survival
31	c.2939G>A, p.Cys980Tyr	c.2333G>T, p.Arg778Leu	Non-severe	Survival
32	c.2719C>T, p.Gln907X ⁴	c.2924C>A, p.Ser975Tyr ²	Non-severe	Survival
34	c.1168A>G, p.Ile390Val	c.2975C>T, p.Pro992Leu, /c.1708-1G>C	Non-severe	Survival
35	c.2157>A, p.Tyr719X	c.3452G>A, p.Arg1151His	Non-severe	Survival
38	c.2333G>T, p.Arg778Leu	c.2333G>T, p.Arg778Leu	Non-severe	Survival
39	c.314C>A, p.Ser105X	c.2620G>C, p.Asn874Pro	Non-severe	Survival
40	c.2333G>T, p.Arg778Leu/c.2310C>G, p.Leu770Leu ^{1,2}	c.3809A>G, p.Asn1270Ser ²	Non-severe	Survival
41	c.3836A>G, p.Asp1279Gly ²	c.2333G>T, p.Arg778Leu ²	Non-severe	Survival

¹c.2333G>T, p.Arg778Leu is a confirmed disease-causing variant. c.2310C>G, p.Leu770Leu is a single nucleotide polymorphism variant linked to

c.2333G>T, p.Arg778Leu. c.2621C>T, p.Ala874Val and c.4072delG, p.Ala1358Profs*35, both of which are confirmed disease-causing variants, are also linked.

²Parental origins confirmed. Variants in left panel, paternal; in right panel, maternal. Patients 4, 7, 8, 25, and 38 were homozygotes. Patient 34 harbored three different variants, without parental origin confirmation. Patient 10, 19, 33, 36 and 37 were not assessed by *ATP7B* sequencing.

³Novel.

⁴*de novo*. *ATP7B* variants were categorized as either severe, including frameshift, nonsense, and classical splice-site variants, or non-severe (all others).

underwent PE, including 4 of 11 with hepatic encephalopathy, bilirubin > 171 $\mu\text{mol/L}$, and obvious hemolysis (1 survived, 1 died, and 2 received LT); 1 of 11 with Grade I encephalopathy after admission with slightly increased bilirubin (who survived), 1 of 11 with progressively increased bilirubin and ammonia (who survived), and 5 of 11 with high bilirubin and obvious hemolysis but without hepatic encephalopathy (4 survived, 1 died). Among them, 3 of 11 patients received continuous veno-venous hemodiafiltration at the same time because of increased creatinine or ammonia levels. Among the 30 patients who did not undergo PE, 1 died without encephalopathy, 1 received LT, and 28 survived including 2 with Grade I-II encephalopathy.

All patients but 2 (who died within 15 d after admission) were treated with D-penicillamine or Zn. Among the 35 patients (35/41, 85.37%) who survived without LT, 33/35 (91.4%) were given D-penicillamine combined with Zn. One failed to tolerate Zn and thus received D-penicillamine alone and 1 received Zn alone because of leukopenia and thrombocytopenia. On follow-up, hematuria appeared in 2 patients, diminishing in 1 patient when D-penicillamine was withdrawn, and persisting even after withdrawal in the other, suggesting the possibility of renal injury.

All 3 patients who underwent LT, including 2 with encephalopathy, have retained their grafts without identified rejection and without obvious neurological symptoms.

Factors associated with poor outcome and mortality in WDALF

Table 2 shows the variables and factors associated with poor outcome and death in the cohort of 41 WDALF patients (6 with poor outcome [3 dying] *vs* 35 surviving). Several variables significantly differed ($P < 0.05$) between these subgroups including encephalopathy, TB, direct bilirubin, gamma-glutamyl transpeptidase (GGT), ammonia, PT, INR, active partial thromboplastin times, fibrinogen, hemoglobin, serum creatinine, and serum sodium. Logistic regression analysis could not demonstrate (too few cases) that any of them was an independent predictor of poor outcome or death. The results of KCHC, MELD/PELD score, LIU score, aLIU score, and Devarbhavi model significantly differed between the survival group and poor outcome group, as did the results between the cohort of those who survived and that of those who died.

***ATP7B* sequencing results and correlation between variants and mortality**

In the 36 of 41 patients (87.8%) in whom *ATP7B* was sequenced, two or more variants were identified, some of which were linked to others, *e.g.*, c.2333G>T (p.Arg778Leu) and c.2310C>G (p.Leu770Leu; **Table 1**). In the 10 patients (27.8%) whose parents were studied, we identified compound heterozygous or homozygous states. Patient 34 interestingly harbored three different *ATP7B* variants (parental studies were not conducted). We identified 33 different variants; the most frequent were c.2333G>T (p.Arg778Leu) and c.2975C>T (p.Pro992Leu), which were present in 17 and 13 patients, respectively. Seven variants were novel, *i.e.* not identifiable in accessible reports or databases. As listed in **Supplementary Table 3**, they were c.2455C>T (p.Gln819X); c.2932_2933insG (p.Val978Glyfs*50); c.2528G>A (p.Gly843Glu); c.2543dupG (p.Asn849Glnfs*5); c.3089G>A (p.Gly1030Asp); c.1529T>C (p.Leu510Pro); and c.1842_1845delins23). All were predictably pathogenic. As categorized, 13 variants were severe (9 nonsense, 3 splice-site, 1 frameshift). Of the 3 patients with biallelic severe variants (8.3%), two survived with therapy alone and the other underwent LT. Two patients who died underwent sequencing; one had biallelic missense variants and the other harbored one nonsense variant and one missense variant. No association between *ATP7B* variant category and clinical characteristics or outcomes was found (**Table 1**).

Different liver disease scoring models for mortality in pediatric WDALF, with AUCs

AUCs of the KCHC, MELD/PELD score, LIU score, aLIU score, and Devarbhavi model are shown in **Table 3** and **4**, and **Supplementary Table 5**, together with sensitivities, specificities, PPVs, and NPVs. C statistics varied from 0.748 to 0.981, with cutoff values those originally reported (*cf.* Methods)[6,7,14-16]. All scoring systems except KCHC had good AUCs (near 1). However, their PPV were < 45% rather than

Table 2 Demographics and baseline clinical characteristics in patients with Wilson disease with acute liver failure with non-transplanted survival (*n* = 35), poor outcome (*n* = 6; 3 dying, 3 surviving after liver transplantation), and dying (*n* = 3)

	Poor outcome group	Survival group	<i>P</i> value	Dying group	Survival group	<i>P</i> value
	<i>n</i> = 6 (14.63%)	<i>n</i> = 35 (85.37%)		<i>n</i> = 3 (7.89%)	<i>n</i> = 35 (92.10%)	
Males (%)	2 (33.33%)	20 (57.14%)	0.390	1 (33.33%)	20 (57.14%)	0.577
Age (yr)	9.82 ± 2.16	10.54 ± 2.60	0.685	11.28 ± 2.17	10.54 ± 2.64	0.465
Jaundice	6 (100%)	26 (74.29%)	0.309	3 (100%)	26 (74.29%)	1.000
Hepatomegaly	2 (33.33%)	8 (22.86%)	0.622	1 (33.33%)	8 (22.86%)	1.000
Splenomegaly	2 (33.33%)	13 (37.14%)	1.000	1 (33.33%)	13 (37.14%)	1.000
Encephalopathy	4 (66.67%)	3 (8.57%)	0.005 ^a	2 (66.67%)	3 (8.57%)	0.040 ^a
Total bilirubin (μmol/L)	452.22 ± 294.19	129.20 ± 175.64	0.007 ^a	395.03 ± 187.16	129.20 ± 175.64	0.021 ^a
Direct bilirubin (μmol/L)	251.27 ± 157.76	75.79 ± 108.91	0.008 ^a	229.77 ± 115.63	75.79 ± 108.91	0.025 ^a
Bile acid (μmol/L)	103.80 ± 96.52	88.61 ± 46.64	0.650	128.87 ± 129.41	88.61 ± 46.64	0.976
ALT (IU/L)	48.67 ± 43.32	61.68 ± 49.13	0.519	74.67 ± 47.44	61.68 ± 49.13	0.432
AST (IU/L)	89.00 ± 26.01	131.24 ± 105.11	0.555	111.67 ± 12.22	131.24 ± 105.11	0.607
GGT (IU/L)	89.67 ± 56.39	159.63 ± 76.06	0.035 ^a	51.00 ± 37.27	159.63 ± 76.06	0.019 ^a
ALP (IU/L)	155.33 ± 147.72	224.19 ± 150.24	0.285	220.67 ± 188.32	224.19 ± 150.24	0.935
Albumin (g/L)	26.93 ± 6.67	25.74 ± 4.23	0.658	28.80 ± 9.20	25.74 ± 4.23	0.343
Total protein (g/L)	56.10 ± 7.80	60.81 ± 7.93	0.249	52.50 ± 5.75	60.81 ± 7.93	0.095
Ammonia (μmol/L)	96.33 ± 26.96	62.65 ± 27.94	0.011 ^a	114.33 ± 25.58	62.65 ± 27.94	0.015 ^a
Serum creatinine (μmol/L)	55.00 ± 47.44	42.24 ± 13.45	0.791	26.33 ± 1.53	42.24 ± 13.45	0.030 ^a
Serum urea nitrogen (mmol/L)	7.75 ± 5.96	3.94 ± 1.20	0.076	4.43 ± 0.95	3.94 ± 1.20	0.386
PT (s)	39.00 ± 15.36	27.04 ± 7.06	0.011 ^a	48.4 ± 17.84	27.04 ± 7.06	0.009 ^a
INR	4.12 ± 2.20	2.53 ± 0.89	0.012 ^a	5.46 ± 2.57	2.53 ± 0.89	0.009 ^a
APTT (s)	74.17 ± 27.70	55.85 ± 12.80	0.042 ^a	90.00 ± 34.01	55.85 ± 12.80	0.028 ^a
Fibrinogen (g/L)	1.03 ± 0.40	1.40 ± 0.41	0.080	0.733 ± 0.23	1.40 ± 0.41	0.014 ^a
WCC × 10 ⁹ /L	11.40 ± 6.54	8.15 ± 4.67	0.203	6.40 ± 2.36	8.15 ± 4.67	0.626
Hemoglobin (g/L)	85.47 ± 19.42	106.41 ± 22.89	0.027 ^a	94.73 ± 19.40	106.41 ± 22.89	0.316
Reticulocyte %	7.78 ± 3.81	4.38 ± 2.72	0.080	7.05 ± 4.10	4.38 ± 2.72	0.136
Platelet count × 10 ⁹ /L	100.33 ± 41.32	109.66 ± 48.01	0.796	69.33 ± 11.59	109.66 ± 48.01	0.129
Serum sodium (mmol/L)	133.83 ± 2.48	136.28 ± 3.28	0.073	132.00 ± 2.00	136.28 ± 3.28	0.029 ^a
Ceruloplasmin (g/L)	0.080 ± 0.002	0.068 ± 0.029	0.082	0.079 ± 0.00	0.068 ± 0.029	0.281
24 h urine copper (μg/24 h)	2563 ± 1915	2083 ± 1964	NA	582.00 ± NA	2083 ± 1964	NA
KCHC	12.00 ± 1.67	8.43 ± 3.42	0.020 ^a	11.33 ± 0.58	8.43 ± 3.42	0.157
MELD/PELD score	31.67 ± 9.87	19.00 ± 7.65	0.007 ^a	38.00 ± 7.00	19.00 ± 7.65	0.006 ^a
LIU-PT score	223.33 ± 63.49	115.77 ± 54.29	0.002 ^a	221.67 ± 45.18	115.77 ± 54.29	0.016 ^a
LIU-INR score	390.67 ± 89.19	217.49 ± 95.36	0.002 ^a	424.33 ± 110.21	217.49 ± 95.36	0.019 ^a
aLIU-PT score	338.50 ± 114.04	160.31 ± 79.75	0.003 ^a	353.00 ± 35.38	160.31 ± 79.75	0.010 ^a
aLIU-INR score	428.17 ± 147.81	189.74 ± 101.95	0.002 ^a	467.00 ± 61.25	189.74 ± 101.95	0.009 ^a
Devarbhavi model score	32.13 ± 18.64	8.59 ± 11.62	0.007 ^a	30.47 ± 10.00	8.59 ± 11.62	0.014 ^a

^a*P* value < 0.05. aLIU: Admission to Liver Injury Unit; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; APTT: Active partial thromboplastin

times; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; INR: International normalized ratio; KCHC: King's College Hospital Criteria; LIU: Liver Injury Unit; MELD/PELD: Model for end-stage liver disease/pediatric end-stage liver disease; NA: Not available; PT: Prothrombin time; WCC: White cell count.

Table 3 Area under the curve and its related indices for comparison of different models predicting mortality in pediatric Wilson disease with acute liver failure

Model	AUC	95%CI			Sensitivity	Specificity	Cutoff value
KCHC	0.748	0.604	-	0.892	1.000	0.714	11.0
MELD/PELD	0.981	0.939	-	1.000	1.000	0.943	31.0
LIU-PT	0.924	0.830	-	1.000	1.000	0.857	175
LIU-INR	0.914	0.795	-	1.000	1.000	0.800	300
aLIU-PT	0.952	0.884	-	1.000	1.000	0.943	290
aLIU-INR	0.962	0.900	-	1.000	1.000	0.943	374
Devarbhavi model	0.933	0.851	-	1.000	1.000	0.914	23.0

AUC: Area under the curve; aLIU: Admission to Liver Injury Unit; KCHC: King's College Hospital Criteria; LIU: Liver Injury Unit; MELD/PELD: Model for end-stage liver disease/pediatric end-stage liver disease.

perfect (Table 4), demonstrating that even some patients assigned high scores using these systems could survive without LT. Among the 3 patients who underwent LT, 2 received scores above cut-off values. Whether the third (patient 2) could have survived with medical therapy alone cannot, of course, now be determined.

Biomarker values were not determined daily in our patients, thus precluding PALF-D scoring (which requires assessment of day-to-day shifts).

DISCUSSION

Even though an international scoring system for WD (developed at the International Wilson Meeting in Leipzig in 2001) exists[2,9,18,19], diagnosing WD during ALF is difficult; yet early diagnosis is important, as WDALF reputedly has a poor prognosis, with high mortality.

To detect K-F rings is speedy and convenient: An experienced ophthalmologist with a slit lamp can do so at any moment. While the K-F ring sensitivity is poor, its specificity can assist with the early diagnosis of WDALF[25]. K-F rings were present in 87.8% of our WDALF patients, which was much higher than the 50% reported in pre-symptomatic patients and in patients with hepatic involvement in all WD patients[9]. This is understandable: Our patients were on average > 10-years-old and were severely ill.

CNHA can be a first manifestation of WD; WD sometimes presents as ALF combined with CNHA or hemolytic crisis, with hemolysis ascribed to high serum copper released from injured hepatocytes. CNHA in children over age 6-years-old or 7-years-old should be investigated for WD[26], and in patients presenting in ALF with CNHA, WD should be considered a possible diagnosis[27]. In a large cohort study of WD, CNHA was found in 42 of 53 patients with WDALF (79.2%)[28]. CNHA was present in 51.2% of our 41 WDALF patients. As serum copper analysis is unavailable at our institute, we cannot comment on hypercupremia as a trigger of CNHA.

Cp levels in WD have been proposed as diagnostic, with an optimal cut-off of 0.14 g/L in clinically ill adult and pediatric WD patients[29], or with an optimal cut-off of 0.2 g/L in asymptomatic WD[30]. However, Cp values may also decrease in non-WD ALF[9,29,30], and vary in WDALF[20]. In an adult and pediatric ALF study (16 WDALF, 124 non-WDALF), a serum Cp value < 0.2 g/L offered only low and unsatisfactory diagnostic sensitivity and specificity[20]. In our study, all WDALF patients had Cp level < 0.2 g/L and only one had Cp level > 0.14 g/L (0.15 g/L).

Collecting urine over 24 h for copper determinations is troublesome and time consuming; the test furthermore is not of value in renal failure, and results in WD can overlap with those in autoimmune hepatitis, chronic active liver disease, or cholestasis,

Table 4 Sensitivity, specificity, and positive and negative predictive values of different mortality-predicting models using their original cutoff values in our pediatric patients with Wilson disease with acute liver failure

	KCHC			MELD/PELD			LIU-PT			LIU-INR			aLIU-PT			aLIU-INR			Devarbhavi model		
	< 11	≥ 11	<i>P</i>	< 30	≥ 30	<i>P</i>	< 153	≥ 153	<i>P</i>	< 297	≥ 297	<i>P</i>	< 173	≥ 173	<i>P</i>	< 212	≥ 212	<i>P</i>	< 10.4	≥ 10.4	<i>P</i>
Cutoff values	< 11	≥ 11	<i>P</i>	< 30	≥ 30	<i>P</i>	< 153	≥ 153	<i>P</i>	< 297	≥ 297	<i>P</i>	< 173	≥ 173	<i>P</i>	< 212	≥ 212	<i>P</i>	< 10.4	≥ 10.4	<i>P</i>
Death (<i>n</i>)	0	3	0.034 ^a	0	3	0.004 ^a	0	3	0.013 ^a	0	3	0.013 ^a	0	3	0.04 ^a	0	3	0.031 ^a	0	3	0.02 ^a
Survival (<i>n</i>)	25	10		31	4		29	7		29	7		25	11		26	10		27	8	
Sensitivity			1.000			1.000			1.000			1.000			1.000			1.000			1.000
Specificity			0.714			0.886			0.806			0.806			0.694			0.722			0.771
PPV			0.231			0.429			0.300			0.300			0.214			0.231			0.273
NPV			1.000			1.000			1.000			1.000			1.000			1.000			1.000

^a*P* value < 0.05. aLIU: Admission to Liver Injury Unit; KCHC: King's College Hospital Criteria; LIU: Liver Injury Unit; MELD/PELD: Model for end-stage liver disease/pediatric end-stage liver disease; NPV: Negative predictive value; PPV: Positive predictive value.

or indeed in ALF of any etiology. In all our patients who underwent this test (*n* = 39), the value was > 100 µg copper/24 h (2133 ± 1940 µg/24 h). Penicillamine challenge testing is not undertaken routinely in our center, due to concern of risk of increased copper release from liver with potential WDALF progression.

Neurological signs and symptoms in WD typically begin in the second or third decade, and are uncommon in children[31]; in critically ill patients, neurological findings may be masked as well[32]. In addition, brain MRI abnormalities considered typical in WD have been found in patients with other chronic liver disease or cirrhosis-associated dysfunction[33].

No single parameter can be used to diagnose WD independently except the detection of two disease-causing *ATP7B* variants, which is of value even in asymptomatic persons and can be considered reliably prognostic[9,34]. Next-generation sequencing can detect both variant alleles in 95% of affected subjects[35], but variants outside coding regions (*e.g.*, those at intron/exon junctions) and deletions can still be missed, and variants of unknown significance pose diagnostic difficulties. In our center, gene sequencing is now rapid and convenient; however, a hurdle is that its cost (nearly US \$300) can discourage caregivers and families alike.

Biomarkers in isolation or in combination have been assessed for utility in early diagnosis of WDALF, including ALP/TB and AST/ATL; cut-off values vary among studies, but can be adjusted to yield good sensitivity and specificity[36]. In our patients, ALP/TB and AST/ALT values ranged widely, and when using cut-off points of ALP/TB < 4 and AST/ALT > 2.2, as used in adult patients[20,36], sensitivity was low. Fluctuations in ALP and AST activities with age perhaps underlie this observa-

tion[37,38]. A combination of 6 to 15 biomarkers is recently described in 24 WDALF patients as affording diagnosis of WD as fast and as accurate as that provided by determinations of Cp and of 24 h urinary copper content[36]. This awaits verification.

In our liver center, 30 to 50 children are diagnosed with WD every year. Those who present as WDALF ($n = 41$ from January 2013 to May 2019; all WD during this interval, ~300) are a minority. This proportion of WDALF among all WD is similar to that in one previous study (5/55, 9%)[4], but is less than those in other reports in which proportions ranged between 23.8% and 63.6%[5-7]. Among our patients with WDALF, 17.1% had hepatic encephalopathy (all grades) at admission, substantially less than the proportions reported in other studies, which ranged from 44.3% to 100%[6,7,11,39]. In addition, encephalopathy among our patients was mild, ranging from Grade I to II. Perhaps relative ease of access to tertiary-institution medical care in China facilitates earlier diagnosis.

The mortality of WDALF was 7.3% in our study (3 patients died) and 7.3% (3 patients) underwent LT. Both values are obviously lower than those in previous studies, with death in 15 of 29 WDALF patients (51.7%) and 10 receiving urgent LT (34.5%)[7], and lacking LT as an option, with death in 33 of 61 WDALF patients (54%)[6]. In a small case series from Japan (5 WDALF patients), none died; three emerged from ALF when given supportive care, one similarly emerged but required LT 6 mo later, and only one underwent urgent LT[5]. Viewed from a different perspective, these three studies also showed respectively that 4 of 29 (13.7%), 28 of 61 (45.9%), and 4 of 5 (80%) patients with WDALF could be rescued with chelator and Zn or trientine therapy (average follow-up, 5-11.8 years). Our observations, with few deaths or urgent LT in WDALF, further support optimism regarding prognosis in WDALF when, as with many patients in our cohort, hepatic encephalopathy is not a complicating factor.

Our three patients who died without LT were severely ill at presentation, as reflected in encephalopathy, high bilirubin and ammonia level, poor coagulation function, low serum sodium levels, low GGT levels, and high MELD/PELD, LIU, and Devarbhavi model scores. Encephalopathy, severe coagulopathy, and bilirubin and ammonia levels are well established as sensitive markers of liver insufficiency in acute and chronic liver failure. Of interest, as possibly less familiar to us, is that GGT and serum sodium were signals of mortality in WDALF. However, these associations could not be further studied here, because too few patients to empower analyses.

All patients who survived ($n = 35$) were given D-penicillamine or Zn, including 3 patients with mild encephalopathy. We observed worsening of neurologic symptoms in none. Zn is increasingly used as first-line therapy for treatment of pre-symptomatic WD patients and as maintenance therapy after initial de-coppering with a chelator, but the efficacy of Zn monotherapy in symptomatic patients with liver disease is still under debate. Treatment failure has been reported in symptomatic children who present with liver disease and in patients whose WD relapse on Zn but improve after reintroduction of a chelator[18]. Our patients received Zn as an auxiliary treatment, excluding 1 patient given Zn alone (allergy to D-penicillamine) after undergoing PE. She survived and recovered. The value of Zn in WDALF patients requires further study.

Extracorporeal liver support systems have been proposed either as a bridge to LT or to assist in recovery from ALF[40]. PE can rapidly and effectively remove free copper from circulation and has been important as a bridge to LT in WDALF[41]. Indeed, PE was such a bridge in 9 of 10 WDALF patients[42]. However, PE and albumin dialysis reportedly also can prevent as well as delay the need for LT[43]. WDALF patients without hepatic encephalopathy can be rescued by PE and medical therapy even without LT[44]. In our study, more patients died or came to LT in the group who underwent PE (2/11 died, 2/11 underwent LT) than in the non-PE group (1/30 died, 1/30 LT); illness was evidently more severe in the PE group.

In our WDALF patients, accuracy differed among the seven assessed scoring systems, with C-statistics values that ranged from 0.748 to 0.981. Aside from the Devarbhavi model, cut-off points were similar to those originally described[6,7,14-16]; we ascribe the disparity to milder encephalopathy in our patients. While those scoring models had good AUCs, their PPVs were not perfect. Thus WDALF children whose disease was classified as severe (with numerical scores above cut-off values) survived without LT, in accordance with others' recent results, which showed that in WDALF with KCHC ≥ 11 or MELD/PELD ≥ 30 survival is possible, with good recovery several months later[5].

After our study was initiated, a prognostic scoring system to predict mortality in PALF was described, with good sensitivity and specificity. This system places particular emphasis on changes in TB and INR during the first few days after PALF is diagnosed[17]. As values for these biomarkers were not determined daily in our

patients, we could not assess performance of this scoring system.

Our single-center retrospective study was limited in some respects. Although a good number of WDALF patients were studied, with *ATP7B* variants identified in most, not enough of them died to permit identification of key predictors of mortality. In addition, only a few WDALF patients in our study manifested encephalopathy, and when present, it was mild in degree.

CONCLUSION

Our pediatric WDALF patients, most of whom harbored *ATP7B* variants, exhibited an overall mortality of 7.3%, showing that pediatric patients with WDALF, including those with milder encephalopathy, can survive and recover well without LT after D-penicillamine and Zn therapy with or without PE. Among seven different prognostic scoring systems, all had good sensitivity but varied in specificity, and PPV was optimal in none. Our results indicate that WDALF with higher scores can be managed initially with administration of chelators and Zn with or without PE, and that patients may recover from ALF even when disease is severe enough to warrant enlisting for LT.

ARTICLE HIGHLIGHTS

Research background

Wilson disease (WD) with acute liver failure (ALF) (WDALF) classically has a high mortality. Many WDALF patients need emergent liver transplantation (LT); however, some WDALF patients do survive without LT. Several prognostic models have been developed to predict ALF or WD mortality, but with varying or contradictory conclusions.

Research motivation

Distinguish WDALF patients who can be spared LT from those in whom LT will be required.

Research objectives

Determine the recent rates in China of mortality and of LT in pediatric WDALF (diagnosis in most patients confirmed genetically) and assess how accurately different prognostic models performed in these patients.

Research methods

Medical records of pediatric WDALF patients in one center over 6 years were retrospectively collected and reviewed. WDALF was confirmed by *ATP7B* sequencing in most patients. Seven different prognostic models were assessed in these WDALF patients (King's College Hospital criteria for end-stage liver disease and for pediatric end-stage liver disease; Liver Injury Unit (LIU) model using prothrombin time (PT) or international normalized ratio (INR); admission LIU model using PT or INR; and Devarbhavi model. Results were evaluated statistically for significance.

Research results

Among 41 Han Chinese patients, WDALF was confirmed in 36 by demonstrating at least two *ATP7B* variants. In the other 5, the diagnosis of WDALF was established by identifying Kayser-Fleischer rings and Coombs-negative hemolytic anemia. In all, 3 died within 15 d of admission, 3 underwent LT within 1 mo of admission, and 3 survived without LT (follow-up 44.6 ± 21.9 mo). Treatment included enteral D-penicillamine and zinc-salt therapy (Zn) with or without urgent plasmapheresis. Eleven underwent plasma exchange (PE), at the same time (2 died, 2 underwent LT, and 7 survived). The other 30 patients did not undergo PE (1 died, 1 underwent LT, and 28 survived). Encephalopathy, coagulopathy, and gamma-glutamyl transpeptidase activity, bilirubin, ammonia, and serum sodium levels were significantly correlated with mortality, but the correlations disappeared on logistic regression analysis. No association between *ATP7B* variant category and clinical characteristics or outcomes was found. Area under the receiver operating curves of the individual models varied from 0.981 to 0.748 with positive predictive values (PPVs) from 0.214 to

0.429.

Research conclusions

Our pediatric WDALF patients, most of whom were found to harbor *ATP7B* variants, exhibited an overall mortality of 7.3%, showing that pediatric patients with WDALF can survive and recover well without LT after D-penicillamine and Zn therapy with or without PE. This is not a novel finding, but it is based on a larger cohort of WDALF patients than reported in any previous study, and the diagnosis of WDALF in these patients—thanks to genetic studies—is more firmly established than in any previous study. Among seven different prognostic scoring systems, all had good sensitivity but varied in specificity, and PPV was optimal in none.

Research perspectives

WDALF with higher scores assigned using various models can be managed initially with administration of chelators and Zn with or without PE, and patients may recover from ALF even when disease is so severe as to warrant listing for LT. However, ours was a retrospective study; prospective studies or prospective cohort studies in pediatric WDALF are underway to reinforce this conclusion. Biomarkers not previously examined can be assessed in these prospective studies to learn if their inclusion improves model performance.

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