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Outcomes of Acute Liver Injury in Adults Due to Wilson's Disease: Is Survival Without Transplant Possible?

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Abstract

Wilson's disease (WD) is a rare cause of acute liver failure (ALF) that is thought to have a uniformly fatal outcome without liver transplantation (LT). Previous studies proposed diagnostic and prognostic criteria for WD-ALF. It is not known whether these apply to WD patients presenting as severe acute liver injury (ALI) without encephalopathy. From 2008 to 2018, 822 patients with ALI in the US Acute Liver Failure Study Group (ALFSG) registry were enrolled and prospectively followed. The diagnosis of WD-ALI was confirmed in 8 patients. Serum biochemical diagnostic ratios predicting WD-ALF (alkaline phosphatase [ALP]: total bilirubin (TB) and aspartate aminotransferase [AST]:alanine aminotransferase [ALT]) were determined in these patients, and predictors of prognosis for WD-ALI were evaluated. Of these 8 ALI-WD patients, 5 received an LT. Ratios of both ALP:TB bilirubin of <4 and AST:ALT of >2.2 on study admission were met in 4 LT patients. All LT patients were female. The Model for End-Stage Liver Disease scores on admission were generally higher in LT patients. All transplanted patients had an initial revised WD score of >11 (>10 predicting poor outcome without LT in WD-ALF), whereas in non-LT patients, 2 had scores of 9, and 1 a score of 13. Also, 3 LT patients were started on chelation therapy, 2 were started on plasmapheresis, and 1 was started on Molecular Adsorbent

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Recirculating System therapy. All non-LT patients were treated with chelation. At 21 days, all patients were alive and discharged from the hospital. In conclusion, some patients with ALI due to WD may survive without LT. Revised Wilson index scores >10 predict poor outcome in most patients with WD-ALI, as they do for WD-ALF, and they correlate positively with the ALI model in this cohort. Biochemical ratios for WD diagnosis appear more applicable to ALF compared with WD-ALI.

Wilson's disease (WD) is a rare cause of acute liver failure (ALF) affecting approximately 2%-5% of patients presenting with ALF.[1,2] WD-ALF is thought to have an almost uniformly fatal outcome without a liver transplantation (LT).[1–3] However, there is a deficit of knowledge of the course of the disease in the patient with WD with acute liver injury (ALI), the precursor to ALF in the natural history of untreated WD. The distinction is critical because the prognosis of ALF due to WD is poor without LT. Our study is unique in capturing a particularly rare cohort of patients presenting with WD-ALI,[4] different from those categorized with ALF due to WD in lacking hepatic encephalopathy. Out of 822 patients with ALI enrolled in the Acute Liver Failure Study Group (ALFSG) registry over a 10-year period, only 1% were found to have confirmed WD-ALI.

Prognostic scoring systems have been developed separately for WD and for all patients presenting with ALI to help identify which patients will have a poor nontransplant survival and who may be rescued with medical therapy.[4] A prognostic score for WD previously developed by Nazer et al.[5] was modified by Dhawan et al.[6] in 2005 in a study that included exclusively pediatric WD patients. This modified score (the revised Wilson index) has proven both sensitive and specific at predicting mortality of ALF and chronic liver failure due to WD without transplantation, and it can therefore help with prognostication and organ allocation in liver failure due to WD. A prognostic score was also developed by the ALFSG, examining all etiologies of ALI, that was based on nearly 400 patients to predict which patients were likely to progress to ALF, LT, or death.[4] However, none of these prognostic scores were specifically developed for WD patients with ALI, and therefore, they require validation for this patient group.

Our primary aim was to describe the clinical course specifically of those enrolled in the registry with WD-ALI, ie, patients with WD with ALI with elevated international normalized ratio (INR) >2 but no encephalopathy, as defined by the ALFSG. This included the risks and predictors of poor patient outcomes, namely, progression to ALF and the need for LT and death, compared with those with a good outcome, which was defined as survival without the progression to ALF or the need for LT. In particular, we hoped to establish whether the existing prognostic scores, including the revised Wilson index[6] and the ALI prognostic score as developed by the ALFSG,[4] can predict a poor outcome in WD-ALI. In doing so, we sought to provide management guidance for this rare patient group with respect to their response to medical treatment, need for LT, and risk of death.

There is no single diagnostic test for WD, and diagnosis relies on the results of a series of clinical, biochemical, and genetic tests. Diagnosis of WD can be difficult in the setting of acute liver disease because of the effect of the acute phase response in the liver on copper parameters and from severe hepatic necrosis and hepatic insufficiency.

Previously defined serum diagnostic criteria for ALF due to WD, ie, ratios of both alkaline phosphatase (ALP):total bilirubin (TB) of <4 and aspartate aminotransferase (AST):alanine aminotransferase (ALT) of >2.2, were determined in all patients from our ALI-WD cohort.[7] A secondary aim of this study was to determine whether these diagnostic ratios apply to WD-ALI in comparison with that previously demonstrated in WD-ALF.[7,8]

Patients and Methods

From September 1, 2008 to December 31, 2018, 822 patients with ALI due to all etiologies were enrolled in the National Institutes of Health–funded ALFSG registry. Patients were recruited from 32 academic centers in the United States and prospectively followed for 21 days. Our study examines all patients found to have confirmed WD-ALI from this cohort according to the Leipzig diagnostic criteria (n = 8).[9,10]

ALI was defined as an acute hepatic illness of <26 weeks with an INR ≥2.0, ALT ≥10 times the upper limit of normal, TB ≥3.0 mg/dL, and the absence of hepatic encephalopathy. This determination of ALI is compared with ALF, which is classically defined as acute onset of illness <26 weeks featuring hepatic encephalopathy (altered mentation to any degree) and moderately severe coagulopathy (INR ≥1.5). Patients in the registry were at least 18 years of age at the time of enrollment, and all patients were hospitalized. Written informed consent was obtained from patients with ALI. All centers complied with their local institutional review boards' requirements and the Health Insurance Portability and Accountability Act. Patient demographics, medical history, clinical features, and laboratory values were collected prospectively at study enrollment, and clinical status and laboratory results were also recorded serially for up to 7 days or until discharge, death, or transplant if prior to 7 days (Table 1). Survival at 21 days was also noted for each enrollee. All data were managed and housed at the Data Coordination Unit at the Medical University of South Carolina.

The principal investigator (PI) at each study site was responsible for collecting a detailed history including demographic data, medical history, social history, and medication history but not limited to prescription drugs, over-the-counter medications, dietary supplements, herbal supplements, xenobiotics, complementary and alternative medicines, and illicit substances. Relevant clinical, biochemical, serological, imaging, and in some cases, histological data were obtained to elucidate the etiology of liver injury. This included serological testing for hepatitis A, B, C, and E; cytomegalovirus; Epstein-Barr virus; herpes simplex virus; and autoimmune hepatitis as well as the metabolic marker serum ceruloplasmin for WD. Patients with known preexisting liver disease other than WD were excluded. We reviewed patients defined by the site PI as having WD-ALI to ensure that the Leipzig criteria for diagnosis were met (Table 2).[9,10] We divided patients with confirmed WD-ALI into those with a poor outcome, namely, progression to ALF, LT, or death, and those with a good outcome who did not progress to ALF and survived without LT.

Serum diagnostic ratios for ALF due to WD (ALP:TB <4 and AST:ALT >2.2) were determined.[7] We calculated predictors of prognosis, including the revised Wilson index[6] and Model for End-Stage Liver Disease (MELD) score, and reviewed parameters that were

predictors of poor outcomes from the ALFSG Natural History of ALI study.[4] We also used a model to predict poor outcome in ALI patients, ie, progression to ALF, LT, or death, using the random forest model first developed by Breiman in 2001.[4,11] Random forest is a statistical method that iteratively develops decision trees or models using binary splits on predictor variables, thus providing a mechanism for estimating the probability that each individual ALI patient will have a poor outcome. A score was determined for each patient, the ALI prognostic score, which predicts the probability of progressing to ALF, transplant, or death (see Table 3). We compared these predictors to known information with respect to mortality. Aspartate aminotransferase-to-platelet ratio index (APRI) scores reflective of fibrosis and cirrhosis were determined in all patients and were correlated with histology results when available.

STATISTICAL CONSIDERATIONS

The Pearson correlation coefficient was used to look for correlations between variables. Tests were performed using Microsoft Excel (Microsoft, Redmond, WA).

Results

Of the 822 ALI patients in the study cohort, 10 (1%) were given the diagnosis of ALI due to WD by the site PI. The diagnosis of WD-ALI, with WD Leipzig diagnostic scores ≥4, was confirmed in 8 patients (median age, 21 years; range, 18-57 years; female, n = 6; see Table 2).[9,10] Two patients with a site PI who determined a diagnosis of WD were excluded from our data analysis because they did not meet the Leipzig diagnostic criteria[9,10] with the available data. However, slit lamp examination and DNA analysis had not been performed on 1 individual, and the second patient was also missing data (including slit lamp, DNA analysis, and liver biopsy) to confirm the diagnosis. A slit lamp examination for Kayser-Fleischer (K-F) rings was performed in all other patients with confirmed WD-ALI. K-F rings were present in 3 of 7 (43%) patients and were inconclusive in 1 patient. Two patients had a diagnosis of previous WD. One patient with a previous diagnosis of WD was first diagnosed at age 16 years but presented with WD-ALI at age 57 years. She reported taking trientine dihydrochloride 5 days a week and reported adherence with her hepatology office visits. The rest of the patients were new presentations with no family history or prior diagnosis of WD. None of the patients with WD-ALI had a history of neurological disease or neurological symptoms at presentation. One patient had a history of depression.

None of the 8 patients presenting with WD-ALI progressed to ALF. A total of 5 of 8 WD-ALI patients underwent LT. All 5 transplanted patients were female, and 2 of 3 nontransplanted patients were male. There was no significant difference in age between transplanted and nontransplanted patients. The median age of transplanted patients was 21 years (range 18-57 years) compared with 19 years (range 19-49 years) in those surviving without transplant. Days from study enrollment to LT ranged from 3 to 14. The serum diagnostic criteria for ALF due to WD, ratios of both ALP:TB of <4 and AST:ALT of >2.2,[7] were met in 4 of 5 LT patients on study admission, but not by the remaining patients.

Prognostic scores for survival were calculated in all patients (see Table 3). Model for End-Stage Liver Disease–sodium (MELD-Na) scores on admission were generally higher in LT

patients versus nontransplanted patients (median, 31 versus 24).[12] All transplanted patients had an initial revised Wilson index of >11 (range, 12-17),[6] whereas in nontransplanted patients, 2 had scores of 9 and 1 had a Wilson index score of 13.

Predictors of poor prognosis determined from the prior study of the natural history of ALI were INR >1.7, bilirubin >3 mg/dL, and jaundice >3 days.[4] Of 8 patients, 5 had jaundice >3 days. All 8 patients had an admission INR >1.7 and bilirubin >3 mg/dL, which are predictive of poor prognosis in ALI.[4] There were 2 LT patients who met all unfavorable ALI prognostic criteria, and the other 3 met 2 out of 3 criteria. Interestingly, the 3 surviving without transplant met all 3 ALI prognostic criteria predicting poor outcome. There was a good correlation between the revised Wilson index score and the ALI predictive model for spontaneous survival ($r = 0.84$; 95% confidence interval, 0.34-0.97).

Explant or biopsy evidence of cirrhosis (n = 4) or fibrosis (n = 1) was found in all transplanted patients. APRI scores were >1 in all ALI-WD patients, which is predictive of significant hepatic fibrosis.[13] There were 3 LT patients who were started on copper chelation therapy, 2 were treated with plasmapheresis, and 1 was treated on Molecular Adsorbent Recirculating System therapy. All patients surviving without transplant (n = 3) were started on copper chelation treatment, but none underwent plasmapheresis. At 21 days after enrollment, all patients were alive and discharged from the hospital. Longterm follow-up data were available for patients who received a LT, except for 1 patient who did not consent for follow-up beyond 21 days. All transplanted patients who had longterm follow-up were alive with no hospital admissions at 12 months of follow-up. All nontransplanted patients were alive at the end of the remaining period of patient consent for study follow-up (median, 6 months; range, 21 days to 23 months).

Discussion

WD is a rare cause of ALF affecting 2%-5% of patients with ALF and is thought to be fatal for most individuals without transplant.[1,2] Severe ALI in WD, ie, WD-ALI not reaching the precise threshold of ALF due to the lack of encephalopathy, has not specifically been studied thus far. In the present study, we were able to confirm the diagnosis of WD-ALI in 8 of 10 patients and noted that contrary to findings with ALF, not all patients with ALI require transplantation. This finding suggests that there is a clear threshold between ALI and ALF that when crossed, changes the opportunity for medical rescue and also suggests that the spectrum of WD with acute and severe presentation is wider than previously realized.

In addition to looking at survival for ALI-WD, we took the opportunity to determine whether the previously identified criteria for the rapid diagnosis of WD-ALF based on standard laboratory tests (ALP:bilirubin of <4 and AST:ALT of >2.2) were applicable to patients with WD-ALI.[7] We found that biochemical ratios for WD diagnosis were more applicable to WD-ALF compared with WD-ALI. The majority of patients who underwent transplantation met the diagnostic serum ratios for WD (4 of 5), whereas none of the patients who survived without transplant met these same criteria. This supposes that the ratios are more useful with increased severity of WD-ALI, which is perhaps not surprising because these individuals would be predicted to have a higher risk of progression to ALF.

The majority of patients with WD-ALI were female (75%), and interestingly, 100% of WD-ALI patients who underwent transplantation were female, suggesting that female sex may predict a worse outcome. There was also less acute kidney injury in our WD-ALI cohort than is seen in ALF due to WD.[14] In trying to predict the outcome for our cohort with ALI due to WD, we examined several prognostic scoring systems for WD and for ALI. Prognostic scoring systems for WD can be critical for facilitating treatment decisions and for risk stratifying which patients can be managed medically or for which patients medical therapy may be futile leaving LT as the only possible rescue therapy. A prognostic score for WD was initially developed by Nazar et al.[5] and modified by Dhawan et al.[6] The revised Wilson index for patients with a score of >10 has previously been shown to predict poor outcomes without LT in WD-ALF.[6] We found that a revised Wilson index score of >10 was also a predictor of poor outcomes in most patients with WD-ALI in our cohort.

To better predict outcomes for this group, we also calculated a score using the ALI predictive model for spontaneous survival, called the ALI prognostic score (see Table 3).[8] There was a good correlation between the revised Wilson index score and the ALI prognostic score for spontaneous survival. In addition, MELD scores on admission were generally higher in those patients in our study group who underwent LT compared with those who did not. Therefore, we suggest that the revised Wilson index, the ALI prognostic score for spontaneous survival, and the MELD score itself are all useful in helping to determine if medical treatment versus LT should be considered in this group. Careful review of the course of these patients over time may allow for discrimination of those who may survive without LT from those who should be transplanted urgently. Future analysis of similar WD ALI patients and comparative analysis of these scores may help determine the score that better discriminates which patients to transplant and what the threshold for the ALI prognostic score for spontaneous survival score should be for clinical use.

A previous study by Koch et al. evaluated the natural history of ALI patients enrolled in the ALFSG registry.[4] During this study, 23% (90/386) of patients with ALI progressed to ALF, LT, or death. The most important variable for determining risk of developing ALF and having a poor outcome was etiology, followed by the reported duration from the onset of jaundice to study admission, acetaminophen level, bilirubin, and INR. Out of 386 patients with ALI, those with ALI due to WD had poorer outcomes; however, this study included only a small number of WD patients (n = 3). Also, the diagnosis was determined by the site investigators and was not subject to full evaluation using the Leipzig criteria as performed in this current study. In our study group, we did find survival in some of the WD patients with medical treatment and supportive care and, therefore, believe that survival is possible in some patients with WD-ALI versus those with WD-ALF in whom survival would be rare despite therapies. However, prognosis in WD-ALI may still be worse than for other etiologies of ALI with 62.5% of WD-ALI patients requiring LT compared with 23% of patients with ALI from the study by Koch et al.[4]

Although we report that some patients with severe ALI due to WD short of ALF can survive without transplantation, there are limitations to this study, and results need to be interpreted with caution. The main limitations of our study are as follows.

The sample size was small, given the rarity of both conditions being investigated.[4] Of the 822 patients with ALI enrolled in the registry over a 10-year period, only 1% of patients had confirmed ALI-WD. Similarly, the study by Koch et al.[4] reported that 3 of 386 patients were found to have WD-ALI. A second limitation is that there is a potential bias of looking at outcomes in ALI where, due to the critical, potentially life-limiting nature of the condition, preallocation of patients into different treatment arms (transplant or nontransplant) is not possible. It is also not possible to retrospectively determine survival of transplanted patients had they not been transplanted. Finally, recognizing ALF or ALI secondary to WD can be difficult because no single test is diagnostic, and diagnosis is based on specific clinical findings, biochemical testing, tissue analysis, and genetic sequencing that support the diagnosis (Leipzig criteria).[9,10] Moreover, in acute liver disease many parameters of copper metabolism used for diagnosis, including serum and urinary copper and serum ceruloplasmin, are less reliable and specific in the context of an acute phase response and severe hepatocellular injury of the liver.[8] K-F rings were present in only 43% of patients in our study, supporting previous data showing that K-F rings are less prevalent in nonneurological WD. Therefore, the diagnosis of some patients with WD may not be captured in this setting if clinical suspicion is not high. A total of 10 individuals were assigned a diagnosis of WD by the site investigator on study entry, and we confirmed WD-ALI in 8 patients who composed the cohort for this study. This indicates that there is uncertainty in making the diagnosis of WD even among experienced clinicians and that incomplete data may limit the ability to retrospectively assign a diagnosis of WD.

In conclusion, patients with ALI due to WD can survive without transplantation, unlike patients with WD-ALF, which is thought to have an almost uniformly fatal outcome. It is important to identify these individuals in order to initiate medical therapy promptly and potentially delay or avoid LT if there is a positive clinical response to therapy. Modified WD scores >10 provide a predictor of poor outcomes in most patients with WD-ALI, as they do for WD-ALF. This score also correlates positively with poor outcomes forecasted by the ALI predictive model for spontaneous survival as well as the risk of mortality due to liver disease conveyed by the MELD-Na score in this cohort. Biochemical ratios for WD diagnosis are more applicable to ALF compared with WD-ALI.

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Abbreviations:

ALF	acute liver failure
ALFSG	Acute Liver Failure Study Group

ALI	acute liver injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APRI	aspartate aminotransferase-to-platelet ratio index
AST	aspartate aminotransferase
INR	international normalized ratio
K-F	Kayser-Fleischer
LT	liver transplantation
MELD	Model for End-Stage Liver Disease
MELD-Na	Model for End-Stage Liver Disease–sodium
NA	not available
PI	principal investigator
TB	total bilirubin
WBC	white blood cells
WD	Wilson's disease

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TABLE 1.

Demographics and Admission Laboratory Values

Patient Number	Sex	Age, years	Transplant	ALT, IU/L	AST, IU/L	ALP, IU/L	TB, mg/dL	INR	Albumin, g/dL	Creatinine, mg/dL	Lactate, mmol/L	Platelets, ×1000/mm^3	Hb, g/dL	WBC, ×1000/mm^3
1	Male	19	No	48	77	47	4.9	2.3	2.2	NA	NA	119	7.6	9.7
2	Male	19	No	52	102	90	4.9	2.6	2	0.55	NA	77	9	4.2
3	Female	49	No	714	585	46	9.5	2.4	1.9	0.7	1.3	159	12.5	6.3
4	Female	57	Yes	44	198	39	10.42	2.17	2.2	0.6	1.8	106	10.2	7.7
5	Female	21	Yes	16	83	25	35	2.5	2.4	0.6	NA	173	8.2	18.4
6	Female	18	Yes	20	125	24	48.1	2.8	2.8	0.82	1.7	195	5.7	16
7	Female	25	Yes	255	364	184	16.7	3.7	2	0.63	NA	46	9.7	10.4
8	Female	20	Yes	52	181	44	11.7	5.4	1.4	0.53	NA	88	9.1	12.4

TABLE 2.

Leipzig Diagnostic Criteria

Patient Number	Leipzig Score*	K-F Rings	Ceruloplasmin, mg/dL	24-Hour Urine Copper, µg	ATP7B Mutation Analysis†	Hemolytic Anemia‡	Liver Copper, µg/g dry weight of liver
1	6	Yes	4	7583	NA	NA	NA
2	7	No	16	3235	Homozygous	NA	NA
3	5	Inconclusive	17	146	1 exon loci	NA	70
4	5	Yes	23	NA	NA	Yes	1122
5	8	Yes	4	4702	Heterozygous	Yes	NA
6	6	No	13	17,210	NA	Yes	1525
7	10	No	9	3991	Homozygous	NA	1374
8	8	Yes	9	1094	NA	Yes	§

*Leipzig score ≥4 establishes a WD diagnosis.

†For the ATP7B mutation analysis, homozygous indicates that 2 identical ATP7B mutations were detected; heterozygous indicates that 2 different ATP7B mutations were detected; and 1 exon loci indicates that 1 ATP7B mutation was detected.

‡From the clinical narrative.

§Quantitation not available. Patchy and strong positive stain.

TABLE 3.

Diagnostic and Prognostic Scores

Patient Number	Sex	Age, years	Transplanted	AST:ALT >2.2	ALP:TB <4	Revised Wilson Index	ALI Prognostic Score	MELD-Na Score	APRI Score
1	Male	19	No	No	No	9	0.53	24	1.6
2	Male	19	No	No	No	9	0.618	23	3.3
3	Female	49	No	No	No	13	0.636	26	9.2
4	Female	57	Yes	Yes	Yes	12	0.668	26	4.7
5	Female	21	Yes	Yes	Yes	15	0.67	31	1.2
6	Female	18	Yes	Yes	Yes	15	0.774	34	1.6
7	Female	25	Yes	No	No	17	0.764	34	19.8
8	Female	20	Yes	Yes	Yes	15	0.8	28	5.1