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Title: Outcomes of acute liver injury (ALI) in adults due to Wilson Disease: Is survival without transplant possible?

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List of Abbreviations:

ALF (Acute Liver Failure);

ALFSG (Acute liver failure study group)

ALI (Acute Liver Injury)

ALP (Alkaline Phosphatase)

ALT (Alanine Transaminase)

APRI (AST to Platelet Ratio Index)

AST (Aspartate Transaminase)

INR (International Normalized Ratio)

LT (Liver transplant)

MELD (Model of end stage liver disease)

Wilson Disease (WD)

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Background: Wilson Disease (WD) is a rare cause of acute liver failure (ALF) 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 (WD-ALI) without encephalopathy.

Methods: From 2008-2018, 822 subjects with ALI in the US Acute Liver Failure Study Group Registry (ALFSG) were enrolled and prospectively followed. The diagnosis of WD-ALI was confirmed in eight. Serum biochemical diagnostic ratios predicting WD-ALF (ALP: bilirubin and AST:ALT) were determined in these patients. Predictors of prognosis for WD-ALI were evaluated.

Results: Five of 8 ALI-WD patients received a LT. Ratios of both ALP: bilirubin of <4 and AST:ALT of >2.2 on study admission were met in 4 LT patients. All LT patients were female. Admission MELD scores 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) while in non-LT patients, 2 had scores of 9 and 1 a score of 13. Three LT patients were started on chelation therapy and 2 on plasmapheresis and 1 on MARS therapy. All non-LT patients were treated with chelation. At 21 days all patients were alive and discharged from hospital.

Conclusions: Some patients with ALI due to WD may survive without LT. Revised WD Index scores >10 predict poor outcome in most patients with WD-ALI, as they do for WD-ALF, and correlate positively with the ALI model in this cohort. Biochemical ratios for WD diagnosis appear more applicable to ALF compared to WD-ALI.

Introduction:

Wilson 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 transplant (LT) (1) (2) (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 since the prognosis of ALF due to WD is poor without liver transplantation. 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 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 non-transplant 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. in 2005 (6) in a study which included exclusively pediatric Wilson Disease patients. This modified score (the revised WD Index) has proven both sensitive and specific at predicting mortality of ALF and chronic liver failure due to WD without transplantation and can therefore help with prognostication and organ allocation in liver failure due to Wilson Disease. A prognostic score was also developed by the Acute Liver Failure Study Group (ALFSG), examining all etiologies of acute liver injury, based on nearly 400 patients to predict which patients are 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 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, patients with Wilson disease with acute liver injury with elevated INR>2 but no encephalopathy, as defined by the ALFSG. This included the risk and

predictors of poor patient outcomes, namely progression to ALF and the need for liver transplantation (LT) and death, compared to those with a good outcome defined as survival without progression to ALF or 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 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 due to 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, ratios of both ALP:TB of < 4 and AST: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 to that previously demonstrated in WD-ALF (7) (8).

Methods:

From September 2008 to the 31st of December 2018, 822 subjects with ALI due to all etiologies were enrolled in the National Institutes of Health (NIH)-funded ALFSG Registry. Subjects 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 Criteria (n=8) (9) (10).

ALI was defined as an acute hepatic illness of <26 weeks with an INR ≥2.0, alanine aminotransferase (ALT) ≥10× upper limit of normal, total bilirubin ≥3.0 mg/dl, and the absence of hepatic encephalopathy. This is compared to acute liver failure (ALF) which is

classically defined as acute onset of illness <26 weeks that features hepatic encephalopathy (altered mentation to any degree), and moderately severe coagulopathy (international normalized ratio (INR) ≥1.5). Patients in the registry were at least 18 years of age at the time of enrolment 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 (HIPAA). Patient demographics, medical history, clinical features, and laboratory values were collected prospectively at study enrolment, 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. Survival at 21 days was also noted for each enrolee. All data was 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, serologic, imaging, and in some cases, histologic 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 pre-existing 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 (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 that did not progress to ALF and survived without LT.

Serum diagnostic ratios for ALF due to WD (ALP: bilirubin <4 and AST: ALT >2.2) were determined (7). We calculated predictors of prognosis including the revised Wilson Index (6) and MELD score and reviewed parameters that were predictors of poor outcome 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 tress, 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 subject, 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. ALT to platelet ratio (APRI) scores reflective of fibrosis and cirrhosis were determined in all patients and 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.

Results:

Of the 822 ALI patients in the study cohort, 10 were given the diagnosis of ALI due to WD by the site PI (1%). The diagnosis of WD-ALI, with WD Leipzig diagnostic scores ≥ 4 (9) (10) was confirmed in 8 patients (median age 21, range 18-57, female n=6) (see table 2). Two patients with a site PI determined diagnosis of WD were excluded from our data analysis as 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 one 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. Kayser-Fleischer rings were present in 3 of 7 patients (43%) 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 but presented with WD-ALI at age 57 years. She reported taking trientine dihydrochloride (trientine) five 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 eight patients presenting with WD-ALI progressed to ALF. Five of eight WD-ALI patients underwent LT. All five transplanted patients were female, two of three non-transplanted patients were male. There was no significant difference in age between transplanted and non-transplanted patients, the median age of transplanted patients was 21 (range 18-57) compared to 19 (range 19-49) 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 four of five LT patients on study admission, but not by the remaining patients.

Prognostic scores for survival were calculated in all patients (see Table 3). MELD-Na scores on admission were generally higher in LT patients (median MELD-Na 31 vs 24) (12). All

transplanted patients had an initial revised WD index of > 11 (range 12-17) (6), while in non-transplanted patients, two had scores of 9 and one had a WD index score of 13.

Predictors of poor prognosis determined from the prior study of the natural history of ALI were INR > 1.7, bilirubin > 3mg/dl and jaundice > 3 days (4). Five of eight patients had jaundice > 3 days. All eight patients had an admission INR > 1.7 and a bilirubin > 3mg/dl which are predictive of poor prognosis in ALI (4). Two LT patients met all unfavorable ALI prognostic criteria, and the other three met 2 out of 3 criteria. Interestingly, the three surviving without transplant met all 3 ALI prognostic criteria predicting poor outcome. There was a good correlation between the revised WD index score and the ALI predictive model for spontaneous survival ((r=0.84) 95% CI 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 predictive of significant hepatic fibrosis (13). Three LT patients were started on copper chelation therapy, two were treated with plasmapheresis and one with MARS. All patients surviving without transplant (n=3) were started on copper chelation treatment but none on plasmapheresis. At 21 days post enrollment all patients were alive and discharged from hospital. Long term follow-up data was available for patients that received a liver transplant, except one that did not consent for follow up beyond 21 days. All transplanted patients that had long term follow up were alive with no hospital admissions at 12 months follow-up. All non-transplanted patients were alive at the end of the remaining period of patient consent for study follow-up (median 6 months (range 21 days-23 months).

Discussion:

Wilson Disease is a rare cause of acute liver failure affecting 2-5% of patients with ALF and is thought to be fatal in most of these individuals without transplant (1) (2). Severe acute liver injury in WD, 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 subjects and noted that, contrary to findings with ALF, not all patients with ALI require transplantation. This suggests, a clear threshold between ALI and ALF that when crossed changes the opportunity for medical rescue, and 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) (7) were applicable to patients with WD-ALI. We found that biochemical ratios for WD diagnosis were more applicable to WD-ALF compared to WD-ALI. The majority of patients who were transplanted met the diagnostic serum ratios for WD (4 of 5) while none of the patients that survived without transplant met these same criteria. This suggests that the ratios are more useful with increased severity of WD-ALI, perhaps not surprising as 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 that were transplanted were female suggesting that female gender 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 risk stratifying which patients can be managed medically or for which medical therapy may be futile and liver

transplant is 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 has been previously shown to predict poor outcome without liver transplantation in WD-ALF patients with a score of >10 (6). We found that a revised WD index score of greater than >10 was also a predictor of poor outcome 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 for our cohort, the ALI prognostic score (see Table 3, reference 8). There was a good correlation between the revised WD index score and the ALI progonostic score for spontaneous survival. In addition, MELD scores on admission were generally higher in those patients in our study group who underwent LT compared to those who did not. Therefore, we suggest that the revised WD index, the ALI prognostic score for spontaneous survival and the MELD score itself all are useful in helping determine if medical treatment versus LT should be considered in this group. Careful review of the course over time in these patients may allow for discriminating those who may survive without LT from those who should be transplanted emergently. Future analysis of similar WD ALI patients and comparative analysis of these scores may help determine which of these are better in discriminating which patient 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 subjects 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 onset of jaundice to study admission, acetaminophen level, bilirubin and INR. Out of 386 subjects with ALI, patients with ALI due to WD had poorer outcomes, however, this study included only a small number of WD patients (n=3), the diagnosis determined by the site investigators and 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 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 other etiologies of ALI with 62.5% of WD-ALI patients requiring LT compared to 23% of subjects with ALI from the study by Koch et al. (4).

While we report that some patients with severe acute liver injury due to WD short of acute liver failure can survive without transplantation, there are limitations to this study; results need to be interpreted with caution. The main limitations of our study are (i) Sample size 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. 2017 reported 3 of 386 patients were found to have WD-ALI. (ii) Potential bias of looking at outcomes in acute liver injury where, due to the critical, potentially life limiting nature of the condition, pre-allocation of patients into different treatment arms (transplant or non-transplant) is not possible. It is also not possible to retrospectively determine survival of transplanted patients had they not been transplanted. Iii) Recognizing ALF or ALI secondary to WD can be difficult as no single test is diagnostic and is based on specific clinical findings, biochemical testing, tissue analysis and genetic sequencing which 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 that they are less prevalent in non-neurological WD. Therefore, the diagnosis of some patients with WD may not be captured in this setting if clinical suspicion is not high. Ten individuals were assigned a diagnosis of WD by the site investigator on study entry and we confirmed WD-ALI in 8 that comprise the cohort for this study. This indicates that there is uncertainty in making the diagnosis of WD even among experienced clinicians, and incomplete data may limit the ability to retrospectively assign a diagnosis of WD.

Conclusion:

Patients with ALI due to WD can survive without transplantation, unlike 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 liver transplant if there is a positive clinical response to therapy. Modified WD scores > 10 provide a predictor of poor outcome in most patients with WD-ALI, as it does for WD-ALF, correlating 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 to WD-ALI.

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Table 1: Demographics and Admission Lab Values

Case no.	Gender	Age (Years)	Transplant (yes/no)	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Total Bilirubin (mg/dl)	INR	Alb (gm/dL)	Cr (mg/dL)	Lactate (mmol/L)	Platelets (x1000/ mm^3)	Hb (g/dL)	WBC (x1000/ mm^3)
1	Male	19	N	48	77	47	4.9	2.3	2.2	Null	Null	119	7.6	9.7
2	Male	19	N	52	102	90	4.9	2.6	2	0.55	Null	77	9	4.2
3	Female	49	N	714	585	46	9.5	2.4	1.9	0.7	1.3	159	12.5	6.3
4	Female	57	Y	44	198	39	10.42	2.17	2.2	0.6	1.8	106	10.2	7.7
5	Female	21	Y	16	83	25	35	2.5	2.4	0.6	Null	173	8.2	18.4
6	Female	18	Y	20	125	24	48.1	2.8	2.8	0.82	1.7	195	5.7	16
7	Female	25	Y	255	364	184	16.7	3.7	2	0.63	Null	46	9.7	10.4
8	Female	20	Y	52	181	44	11.7	5.4	1.4	0.53	Null	88	9.1	12.4

Table 2: Leipzig Diagnostic Criteria

Case no.	Leipzig score for WD diagnosis**	K-F rings	Ceruloplasmin (mg/dl)	24 hr urine copper (μg)	ATP7B Mutation analysis	Hemolytic Anemia*	Liver Copper (μg/g dry wt liver)
1	6	Yes	4	7583	null	n/a	null
2	7	No	16	3235	Homozygous	n/a	null
3	5	Inconclusive	17	146	One exon loci	n/a	70
4	5	Yes	23	null	null	Yes	1122
5	8	Yes	4	4702	Heterozygote	Yes	null
6	6	No	13	17210	null	Yes	1525
7	10	No	9	3991	Homozygous	n/a	1374
8	8	Yes	9	1094	null	Yes	***

ATP7B Mutation Analysis

Homozygous: Two identical ATP7B mutations detected
Heterozygous: Two different ATP7B mutations detected
One exon loci: One ATP7B mutation detected.

*From clinical narrative
** Leipzig score ≥4 WD established
*** quantitation not available, patchy, strong positive stain
Null = data not available

Table 3: Diagnostic and Prognostic Scores

Case no.	Gender	Age	Transplanted	AST/ALT >2.2	ALP/TB <4	Modified WD	ALI Prognostic	MELD-Na	APRI Score

						Score	score	Score	
1	Male	19	N	N	N	9	0.53	24	1.6
2	Male	19	N	N	N	9	0.618	23	3.3
3	Female	49	N	N	N	13	0.636	26	9.2
4	Female	57	Y	Y	Y	12	0.668	26	4.7
5	Female	21	Y	Y	Y	15	0.67	31	1.2
6	Female	18	Y	Y	Y	15	0.774	34	1.6
7	Female	25	Y	N	N	17	0.764	34	19.8
8	Female	20	Y	Y	Y	15	0.8	28	5.1

Y = Yes

N = N