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ORIGINAL ARTICLE

Plasma exchange improves survival with native liver in Wilson disease with new Wilson's index ≥ 11 & early hepatic encephalopathy

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Abstract

Background and aim Decision about liver transplant is difficult in Wilson disease (WD) with liver failure, especially with conflicting reports about new Wilson index (NWI). Therapeutic plasma exchange (TPE) can provide survival with native liver (SNL) in WD. This study was done to see the effect of TPE on outcome and identify factors for SNL.

Methods All cases of WD with liver failure (INR. ≥ 2.5) from prospectively maintained data were included for propensity score matching (PSM) to select TPE ($n = 48$) and no-TPE ($n = 48$) groups. Three sessions of TPE on three consecutive days were given to TPE group.

Results One hundred fifty-nine cases were included in the PSM with NWI & hepatic encephalopathy (HE) grading as predictors. SNL was comparable (26 vs. 17 cases (OR 1.45, $p = 0.05$) when the analysis was done in the whole cohort of 96 patients. SNL significantly improved when performed in those with no to early HE: TPE group (24/37) versus no-TPE group (14/34) (OR = 1.70, $p = 0.03$). Kaplan–Meier survival curves were significantly (log rank 0.019) improved in the TPE group when analyzing in no to early HE. Lower INR (adjusted OR 0.47, 95%CI 0.28–0.79, $p = 0.005$) and TPE administration (adjusted OR 3.12, 95%CI 1.10–9.4, $p = 0.032$) at enrollment were independently associated with SNL. Lower NWI (adjusted OR 0.686, 95%CI 0.53–0.89, $p = 0.005$) at 96 h was independently associated with SNL.

Conclusions TPE is independently associated with improvement in SNL by threefold in patients with NWI ≥ 11 and no to early HE. Patients with advanced HE should be offered immediate liver transplant. After 3 sessions of TPE, NWI < 11 increases SNL by 32%. Hence, NWI should be maintained below 11 with more sessions of TPE.

Keywords Wilson disease · New Wilson index · Survival with native liver · Therapeutic plasma exchange

Introduction

Wilson disease (WD), also known as hepatolenticular degeneration, accompanied by chronic liver disease (CLD) or cirrhosis, is caused by mutation of *ATP7B*. The *ATP7B* protein is synthesized in the endoplasmic reticulum and relocates to the trans-Golgi network due to copper-induced trafficking in the hepatocytes. The biosynthetic function of *ATP7B* is to load copper into the ceruloplasmin which removes copper through endocytosis to the blood. Mutation of the ATP7B gene causes copper accumulation in liver. WD is one of the few treatable diseases where prognosis depends on early institution of copper chelation therapy before irreversible liver damage occurs. The common therapeutic strategy is the use of chelating agents (d-penicillamine and trientine) and zinc which decreases absorption of copper. In 2005, new Wilson index (NWI) was derived from 74 children with WD.

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As can be seen in Supplementary Fig. 1, NWI is a calculated score from the values of serum bilirubin, serum albumin, international normalized ratio, aspartate aminotransferase (AST), and white cell count (WCC). A calculated score of ≥ 11 of NWI had the sensitivity of 93%, the specificity of 98%, and the positive predictive value of 88% for predicting mortality without liver transplantation (LT) [1]. Some researchers [2] have raised doubts about the prognostic efficacy of NWI. Due to rapid removal of copper, therapeutic plasma exchange (TPE) can provide native liver survival benefits in WD. Nonrandomized study in children with WD reported significantly higher transplant-free survival 9/19 (47.3%) in TPE group vs standard medical treatment group 3/18 (16.6%) (OR 2.84, 95% CI 0.91–8.8, $p = .049$) [3]. Subsequently (2023) in the guidelines by the American Society for Apheresis, WD was listed as category I indication for TPE [4]. This study compared the survival with native liver at 90 days in propensity matched Wilson disease presenting with INR > 2.5 and NWI ≥ 11 with and without therapeutic plasma exchange.

Methods

This was a propensity score-matched analysis composed of children with WD with INR > 2.5, aged less than 18 years, admitted in the department of Pediatric Hepatology from January 2011 to May 2024. All patients showed an evidence of chronic liver disease and 75 fulfilled the Asia Pacific Association of Study of the Liver (APASL) definition of acute on chronic liver failure (ACLF) [5]. Rest 21 were labeled as chronic decompensated liver disease. All these patients could not fulfill the Pediatric Acute Liver failure (PALF) definition due to the presence of chronic liver disease [6]. The study protocol was approved by the institutional ethics committee. Data were retrieved from a prospectively maintained database of patients. All patients with suspected liver disease underwent detailed etiologic work-up, including WD, viral, autoimmune, metabolic, vascular, and histological evaluation as applicable. Diagnosis of WD was based on Leipzig score [7]. All patients had Kayser–Fleischer (KF) rings evaluation by slit lamp by a single experienced ophthalmologist. Hepatic encephalopathy (HE) grading was done as per the West Haven Classification [8]. For those in no to early HE (i.e., grade 1 or 2), slit lamp was performed. Till 2020 December, 5 common and known mutations of WD (448–452, 813 C > A, 3182 G > A, 3305 T > C, 1708–1 G > C) were performed singularly to confirm positive mutational analysis (1 homozygous or 2 heterozygous). Since January 2021, the patients underwent whole-exome sequencing or target gene analysis for the confirmation of the diagnosis. Serum ceruloplasmin was performed by nephelometric method using Dade Behring BN ProSpec system. Urinary copper estimation was determined with the atomic absorption spectrophotometry. Coombs negative hemolysis was defined as reticulocyte count > 2.5%, target cells present in peripheral smear and direct Coombs test negative.

Therapeutic plasma exchange

TPE was administered to all the WD patients with INR > 2.5 patients, with or without the presence of HE and hemolysis since 2015. WD patients who either attended this center from 2011 to 2014 or those who did not consent for TPE in the period 2015–2024 were continued on standard medical therapy and were labeled as no-TPE group. TPE was performed using the Spectra Optia Apheresis System (Terumo BCT, Lakewood, Colorado, United States), which is based on the continuous flow centrifugation principle. A volume equivalent to 1.5–2 times the calculated plasma volume based on the weight of the child was exchanged in a single session. Fresh frozen plasma was used as replacement fluid and estimated plasma volume was calculated based on the following formula: Plasma volume = Blood volume (1 − Hematocrit/100) where blood volume = 80 mL/kg.

After consent, the protocol included three sessions of TPE on three consecutive days and was performed via double-lumen venous access through the internal jugular vein. The decision to do 3 sessions consecutively was as per the previous experience of the authors. Both TPE and no-TPE group received the standard treatment including D-penicillamine/trientine (copper chelation drugs) along with zinc as per the departmental protocol [5]. To avoid significant loss of the copper chelation drugs, the drug was given after completion of TPE session. Hemodynamic, physiological, and neurological status and laboratory data (electrolytes, blood gasses, bilirubin, albumin, INR, complete blood count) were closely monitored immediately before commencing and 24 h after third/last session of TPE and recorded. Ionized calcium levels were measured hourly and the calcium infusion was titrated to maintain ionized calcium of 1 mmol/L. Anticoagulant citrate dextrose solution A was utilized to prevent clotting in the extracorporeal circuit and delivered at 0.4 times the anticoagulant flow rate in mL per hour. The rest of the details have been published in the methodology of two earlier works from this center [3, 9].

Liver atrophy was defined as liver size below 11 mm on ultrasound abdomen where liver was imaged in both the transverse (or sagittal) and the longitudinal (or axial) planes. The liver size was the craniocaudal diameter of the right lobe measured from the top of the liver under the diaphragm to the inferior border of the liver in the midclavicular line. All patients were managed as per the department protocol given in an earlier publication [3, 5]. As per the departmental protocol, intravenous albumin

was administered to those with serum albumin levels < 2.5 mg/dl. And fresh frozen plasma is administered to those bleeding. As per the NWI ≥ 11, these patients were listed for LT and donor evaluation was initiated. As mentioned before, 3 consecutive TPE sessions were planned in the next 72 h, hence comparing the parameters 24 h after the 3rd session of TPE (at 96 h). Any further session of TPE administered, between 96 h and 28 days, was at the discretion of the treating clinician keeping the same indications for TPE. No-TPE sessions were administered after 28 days. Contraindication for TPE was septic shock and criteria for clinical improvement were INR < 2.5, NWI < 11, and no-HE. Hence, if there was clinical improvement present for 24 h after the second TPE, the third session of TPE was not performed. If there was advanced HE and/or INR > 4.5, at presentation or anytime later in the hospital, LT was offered immediately. If patients did not show improvement after the first TPE, the donor work-up and the authorization were completed, and the donor was kept ready as standby. In case of delay in LT or if the family refused LT, we continued with TPE till either LT or contraindication to TPE or clinical improvement (INR < 2.5 or NWI < 11) happened in the patient. No patient was denied LT if they gave consent and arranged logistics for the surgery.

The patients were discharged once INR < 2.5 & NWI < 11 and recovered from HE. Follow-up was done every 1–2 weeks till the ascites (if present) were resolved on abdominal ultrasonography and thereafter monthly. If the patient was found to have 2 consecutive values of INR > 2.5 24 h apart on follow-up, or NWI ≥ 11 or HE, he was again admitted for TPE. Numbers of TPE procedures were decided based on INR value > 2.5/NWI ≥ 11 or HE on subsequent days. After the normalization of serum bilirubin, transient elastography was done to measure the liver stiffness every 6 months.

Propensity score matching (PSM) to identify controls for non-intervention arm

PSM was used to identify a matched cohort of patients from those receiving and not receiving TPE. In the first step, we selected all cases with INR ≥ 2.5. Propensity score automated matching was performed using the Statistical Package for Social Sciences (SPSS) version 27. Controls were selected from the non-intervention group in a 1:1 ratio using predictors NWI ≥ 11 and HE grade with matching tolerance of 0.02. The balance of the two cohorts (TPE and no-TPE arms) post-matching was confirmed by comparing the selected variables.

Outcome measures

The primary outcome measure was Survival with Native Liver (SNL) in WD with INR > 2.5 on day 90 with and without TPE. The secondary outcome measures included comparison of clinical and biochemical parameters [HE, bilirubin, international normalized ratio (INR), albumin, ammonia] in with or without TPE at enrollment and at 96 h after enrollment.

Statistical analysis

The data were analyzed using SPSS version 27. Continuous variables are expressed as median (IQR) and categorical/discrete variables as percentages or frequencies. Continuous variables were compared between the two groups using an independent samples *t* test, whereas categorical variables were compared using chi-square test or Fisher's exact test. Logistic regression analysis was used to identify predictive risk factors for poor outcome WD with liver failure with or without TPE. Kaplan–Meier analysis was done to compare the survival of those with HE grade 3 or 4 versus those without. The analysis was performed in 2 models: Models 1 and 2. In Model 1, we excluded all patients with advanced HE grade at enrollment ($n = 25$) and attempted logistic regression analysis on 71 patients to identify independent predictive factors at enrollment for SNL at 90 days. In Model 2, all the predictive factors at 96 h showing association (on univariate analysis) with SNL at 90 days were included to perform logistic regression analysis for identifying independent predictive factors for SNL at 90 days. In Model 2 also, all advanced HE patients at 96 h were excluded ($n = 38$) and logistic regression analysis was attempted with sample size of 58.

Results

Of the 179 cases of WD with liver failure (INR > 2.5), 20 patients were excluded since 14 either died or were transplanted within 48 h of hospital stay and 6 had septic shock at admission (Fig. 1). Remaining 159 were included in PSM. Median Leipzig score of the cohort was 5.5 (IQR 4–7). Of the 51 cases of TPE, for 8 cases, the treating clinician had taken the decision to not give the third session of TPE as the patient continued to show clinical improvement after 2 sessions of TPE. Hence, of the 51 patients, eight had received at least 2 sessions and the rest had received at least 3 sessions of TPE. On performing PSM between TPE and no-TPE groups, with NWI ≥ 11 & HE grading as predictors, 96 patients (48 in the TPE group and 48 in No-TPE group) were selected with match tolerance of 0.02. Only 6 of the 75 patients with acute on chronic liver failure were hepatitis A

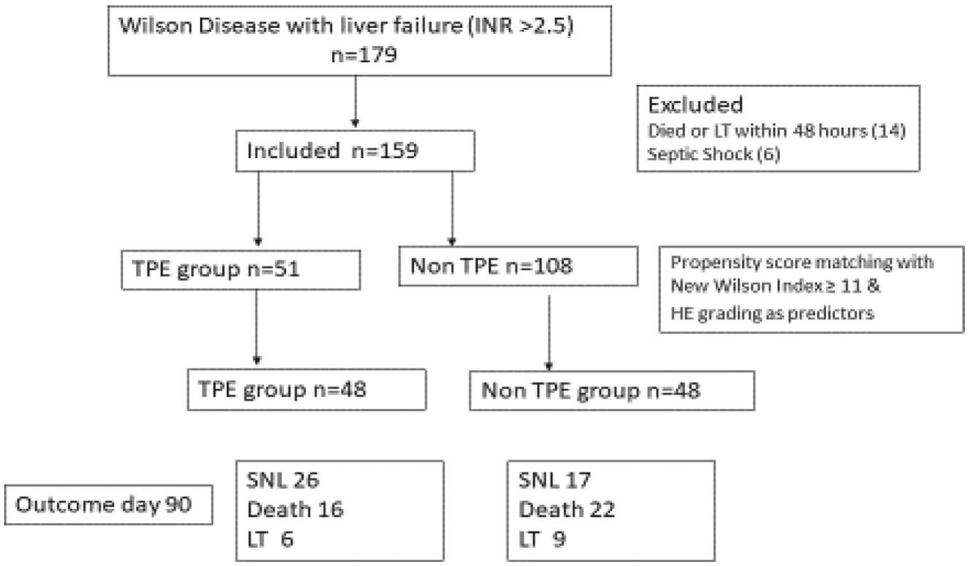


Fig. 1 Flow diagram of the cohort of Wilson's disease

virus infection positive and none had any other hepatotropic viral infection or hepatotoxic drugs as the acute precipitant. Of the whole cohort, 39/48 patients in No-TPE group, 31/48 cases in the TPE group received albumin administration, but no patient received fresh frozen plasma. All the 96 patients had Leipzig score ≥ 4 and 63/96 were genetically proven WD.

After propensity score matching

Median age of the children was 104.50 months (IQR from 84 to 132 months) with male preponderance (57, 59.4%). Jaundice was the presenting symptom in 90/96 patients. Median weight z score and height z score were 0.37 (IQR − 1.38–0.26) and 0.57 (− 1.41–0.5) with ascites present in 77/96 (80.2%): majority had grade 1 ascites identified on ultrasound abdomen. Liver atrophy was present in 39/96 cases. HE grades 3 and 4 were present in 25 (26%) of 96: 33 (34.3%) had no-HE and 38 (39.5%) cases had HE grade 1 or 2 (early HE). Median (IQR) values serum bilirubin, INR, TLC, albumin, and NWI were 20.8 (7.2–30.5 mg/dl), 3.5 (2.88–4.72), 11 (7.8–16.8 per mm^3), 2 (1.8–2.5 g/dl), and 14 (12–17) respectively in the cohort of 96. Coombs negative hemolysis was present in 75 (78.1%) cases. Table 1 depicts the baseline comparison between TPE and no-TPE group. Except reticulocyte count (3.74 vs. 3, *p* value 0.04), all other baseline data were comparable between the two study groups. Significantly higher reticulocyte count was seen in the TPE group.

Comparison of the two study groups

Of the 48 cases in the TPE group, median sessions of TPE received were 3(IQR 3–4 (Table 1). TPE also led to a significant improvement in INR, serum albumin, HE grade, and NWI 24 h after the 3rd TPE session (Table 2). SNL in the two study groups was comparable (26 vs. 17 cases (OR 1.45, $p = 0.05$), but significantly improved when we excluded the advanced HE cases from TPE (excluded cases were 11) and no-TPE (excluded cases were 14) arms. Hence, in cases with no to early HE (excluding cases with advanced HE grade), SNL was significantly more in the TPE versus no-TPE group (25/37 vs. 14/34, OR = 1.70, $p = 0.03$) (Table 2). Twenty-four hours after the 3rd TPE session, 25 cases had advanced HE and 71 had no to early HE. SNL was seen in 2 of the 25 with advance HE and 39 of the 71 with no to early HE. The survival comparison of the two is seen as Kaplan–Meier survival curves in Fig. 2A and B. The survival was significantly (log rank 0.019) improved in the TPE group when analyzing those with no to early HE. Adverse events including the post-TPE platelet count in the TPE group versus no-TPE group are comparable as depicted in Supplementary Table 1.

Predictive factors at enrollment for survival with native liver at 90 days

On comparison with univariate analysis of clinical and biochemical parameters to identify the predictive factors for SNL, lower median bilirubin (mean difference = 6.48, 95%CI 7.2–12.2, $p = 0.028$), lower median INR (mean difference = 1.23, 95%CI 0.66–1.79, $p < 0.001$), lower median NWI (mean difference = 1.6, 95%CI 0.52–2.69, $p = 0.004$), absence of HE grade 3 or 4 (OR = 2.04, 95%CI 1.54–2.71, $p < 0.001$), and presence of TPE (OR = 3.12, 95%CI 1.34–7.26, $p = 0.013$) were associated with SNL. All the above-mentioned factors were entered in Model 1 to identify predictive factors for SNL. As mentioned, in

Table 1 Comparison of baseline data after propensity matching

	TPE $n=48$	No-TPE $n=48$	Effect size (95%CI)	p value
Median age in months (IQR)	104.5 (84–131)	104.5 (79–138)	MD = − 1.97 (− 15.7–11.8)	0.776
Gender (males)	29	28	OR = 0.966 (0.69–1.34)	1.00
Median weight Z score (IQR)	− 0.27 (− 1.47–0.41)	− 0.58 (− 1.37–0.18)	MD = 0.176 (− 0.24–0.59)	0.410
Median height Z score (IQR)	− 0.54 (− 1.59–0.64)	− 0.60 (− 1.26–0.48)	MD = − 0.076 (− 0.62–0.47)	0.783
Median serum Bilirubin (mg/dl) (IQR)	22.9 (7.6–30.45)	20.4 (6.2–30.5)	MD = 2.65 (− 3.1–8.44)	0.366
Median INR (IQR)	3.55 (2.88–4.57)	3.48 (2.7–4.82)	MD = 0.095 (− 0.51–0.70)	0.757
Median serum albumin (g/dl) (IQR)	2.26 (1.80–2.56)	2 (1.82–2.17)	MD = 0.27 (− 0.042–0.57)	0.091
Median TLC (per mm^3) (IQR)	10.5 (6.4–17.3)	12.4 (7.5–15.8)	− 0.88 (− 3.5–1.88)	0.521
Median AST (IU/L) (IQR)	183 (133–225)	171 (131–233)	− 64 (− 161–32)	0.186
Presence of hemolysis	39	36	OR = 0.923 (0.74–1.14)	0.622
Median reticulocyte count (%) (IQR)	3.74 (2.5–6.5)	3 (1.52–4)	1.24 (0.06–2.43)	0.040
Median hemoglobin (mg/dl) (IQR)	7.6 (5.9–9.5)	8 (7–10)	MD = 0.46 (− 1.5–0.58)	0.382
Median platelets (per mm^3) (IQR)	131 (75–191)	137 (100–165)	− 4.0 (− 41–33)	0.834
Median serum creatinine (mg/dl) (IQR)	0.4 (0.3–0.8)	0.3 (0.03–0.73)	0.12 (0.19–0.4)	0.476
Presence of ascites	37	40	1.23 (0.69–2.18)	0.609
Presence of liver atrophy	20	19	1.044 (0.69–1.56)	1.000
HE grade 3/4	11	14	OR = 1.38 (0.55–3.46)	0.642
Median NWI (IQR)	14.50 (11–16.75)	14 (12–17)	MD = 0.125 (− 1.24–0.995)	0.825
Median TPE sessions (IQR)	3 (3–4)	None	NA	NA
Sessions (number of cases)				
2–4	40			
5–6	6			
9	2			

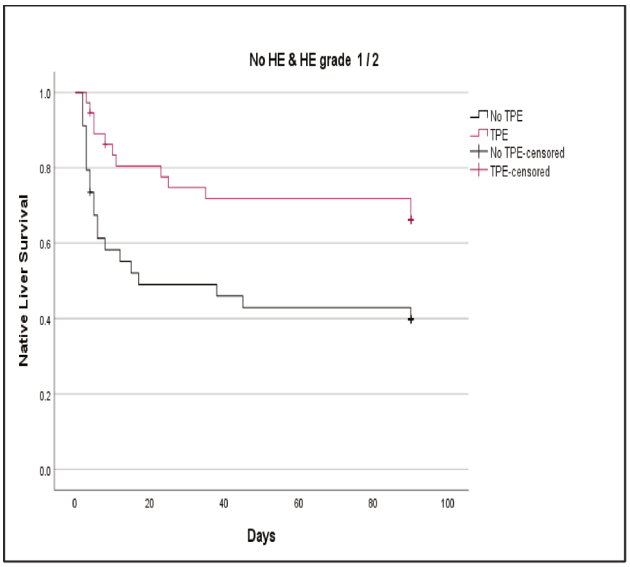
TPE therapeutic plasma exchange; *MD* mean difference; *OR* odd's ratio; *TLC* total leucocyte count; *AST* aspartate transaminase, *HE* hepatic encephalopathy; *NWI* New Wilson index

Table 2 Comparison of the biochemical data after the last 3rd TPE session (at 96 h) and outcome at 90 days

	TPE $n=48$	No-TPE $n=48$	Effect size (95%CI)	p value
Median total bilirubin (mg/dl) (IQR)	10.2 (5–19.7)	12.5 (6–25	MD = 2.65 (− 3.1–8.44)	0.483
Median INR (IQR)	2.4 (1.94–3.5)	3.15 (2.25–4.4)	MD = − 0.93 (− 1.55 to− 0.29)	0.004
Median albumin (g/dl) (IQR)	2.82 (2.5–3.01)	2.15 (1.91–2.52)	MD = 0.496 (0.28–0.70)	< 0.001
HE grade 3/4	14	24	OR = 2.42 (1.05–5.63)	0.03
Median NWI (IQR)	11 (9–14)	13 (10–16.25)	MD = − 2.13 (− 3.51 to − 0.75)	0.003
Hospital stay (days) (IQR)	10 (5–18)	3 (5–15)	MD = 3 (− 2.4–8.42)	0.275
Survival with native liver at 90 days in the whole cohort (%)	26 (54.16%)	17 (35.4%)	OR = 1.45 (0.976–2.175)	0.05
Death	16	22		
LT	06	09		
Survival with native liver at 90 days in those with HE grade 1/2 or no-HE at baseline	25/37* (67.5%)	14/34** (41.12%)	OR = 1.70 (1.03–2.83)	0.033
Death	09	18		
LT	03	02		

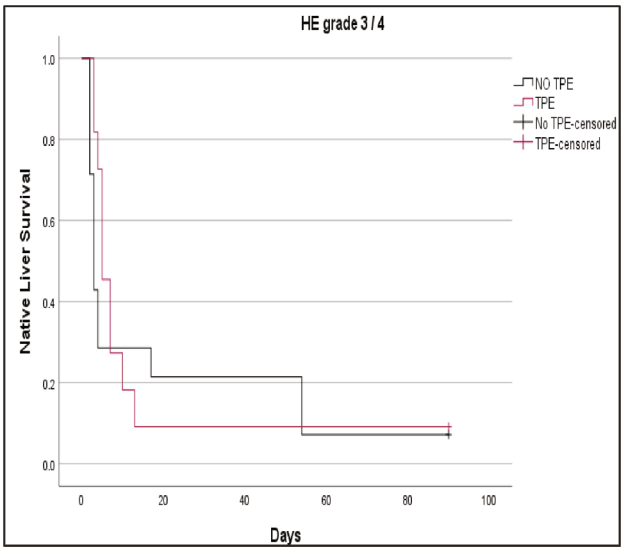
TPE therapeutic plasma exchange; *MD* mean difference; *OR* odd's ratio; *HE* hepatic encephalopathy; *NWI* new Wilson index; *LT* liver transplantation

*$n=37$ **$n=34$: these are the number of cases with no to early HE



Log rank (mantel Cox) Chi Square 5.52, Significance 0.019

a



b

Fig. 2 **a** Kaplan–Meier survival curve depicting the survival with native liver in TPE versus No-TPE group in cases with no-HE & HE grade 1 or 2. **b** Kaplan–Meier survival curve depicting the survival with native liver in TPE versus No-TPE group in cases with HE grade 3 or 4

methodology section, all patients with advanced HE grade at enrollment ($n=25$) were excluded for logistic regression analysis in Model 1 ($n=71$). Lower INR (adjusted OR 0.47, 95%CI 0.28–0.79, $p=0.005$) and TPE (adjusted OR 3.12, 95%CI 1.10–9.4, $p=0.032$) at enrollment were found to be independently associated with SNL (Table 3). The Model 1 improved the overall classification of the outcome from 65.8 to 76.7%.

Predictive factors at 96 h for survival with native liver at 90 days

By 96 h, 2 or 3 sessions of TPE were completed for the TPE group and 2 patients, and one each with early HE & advanced HE had died in the non-TPE group. Hence, only 94 cases were alive at 96 h. Advanced HE at enrollment increased from 25/96 cases to 38/94 at 96 h: 14 additional

Table 3 Univariate and multivariate analysis to identify predictive factors for survival with native liver at enrollment and at 96 h

	SNL $n=41$	Death/LT $n=55$	Effect size (95%CI) p value	Model 1 at enrollment $n=71$# LRA	Model 2 at 96 h $n=70$## LRA
Median Total Bilirubin At enrollment At 96 h** (mg/dl) (IQR)	9.3 (3.3–27.9) 7.9 (2.7–14.7)	25 (9–31) 16.7 (8.6–25.3)	MD = 6.48(7.2–12.2) 0.028 MD = 7.46(2.97–11.95) 0.001	NS NA	NA NS
Median INR At enrollment At 96 h** (IQR)	3 (2.49–3.51) 2.17 (1.87–2.6)	4(3.27–5.65) 3.6(2.5–4.76)	MD = 1.23(0.66–1.79) < 0.001 MD = 1.63(1.07–2.2) < 0.001	Adj OR = 0.47 (95%CI 0.28–0.79) $p=0.005$	NA NS
Median Albumin At enrollment At 96 h** (g/dl) (IQR)	2.1(1.9–2.5) 2.5(2.15–2.9)	2(1.8–2.35) 2.5(2–2.9)	MD = 0.26(− 0.04–0.57) 0.095 MD = 0.12(− 0.11–0.36) 0.304	NA NA	NA NA
No-HE to HE grade 1/2 At enrollment At 96 h**	39 40	32 18	OR = 2.04 (1.54–2.71) < 0.001 OR = 3.13 (2.13–4.62) < 0.001	NA NA	NA NA
Presence of hemolysis	30	45	OR = 1.31 (0.80–2.14) 0.330	NA	NA
Presence of sepsis	19	30	OR = 0.82 (0.52–1.31) 0.536	NA	NA
Presence of ascites	34	43	OR = 1.19 (0.63–2.27) 0.614	NA	NA
Presence of liver atrophy	15	24	OR = 1.13 (0.80–1.59) 0.533	NA	NA
Median NWI At enrollment At 96 h** (IQR)	13(11–15) 10(8–12)	15 (13–17) 15 (11–17)	MD = 1.6(0.52–2.69) 0.004 MD = 4.24(3.08–5.48) < 0.001	NS NA	Adj OR = 0.686 (95%CI 10.53–0.89) $p=0.005$
TPE given	27	21	OR = 3.12 (1.34–7.26) 0.013	Adjusted OR = 3.19 (95%CI 1.10–9.4) $p=0.032$	NA

SNL survival with native Liver; *LT* liver transplant; *LRA* logistic regression analysis; *MD* mean difference; *HE* hepatic encephalopathy; *NWI* New Wilson index; *TPE* therapeutic plasma exchange; *NS* not significant; *NA* not applicable

**$n=53$ for the Death/LT group since 2 patients died within 96 h, #$n=71$ excluding patients with HE grade 3 & 4, ##$n=70$ since one patient with HE grade 2 died within 96 h,

cases shifted from no to early HE subgroup to advanced HE. Significantly higher numbers of cases with no to early HE progressed to advanced HE by 96 h in non-TPE group: 3/37 in TPE group versus in 11/34 in No-TPE (OR 4.45, 95%CI 1.16–17.2, $p=0.040$). At 96 h, 58/94 cases were in no to early HE subgroup and this cohort was used for univariate and logistic regression analysis. On univariate analysis, lower median bilirubin (mean difference = 7.46, 95%CI 2.97–11.95, $p=0.001$), lower median INR (mean difference = 1.63, 95%CI 1.07–2.2, $p<0.001$), lower median NWI (mean difference = 4.24, 95%CI 3.08–5.48, $p<0.001$), and no to early HE (OR = 3.13, 95%CI 2.13–4.62, $p<0.001$) were associated with SNL. All the above-mentioned factors were entered in Model 2 to identify predictive factors for SNL at 96 h. Lower NWI (adjusted OR 0.686, 95%CI 0.53–0.89, $p=0.005$) at 96 h was found to be independently associated with SNL (Table 3). The Model 2 improved the overall correct classification of the outcome from 71 to 75%. Of the 48 cases in TPE group, 31 received either two ($n=8$) or three ($n=23$) TPE sessions and 17 cases received 4–9 sessions of TPE between 96 h and 28 days. 6 and 5 cases of the 17 (who received 4–9 sessions of TPE) had advanced, early, and no-HE at 96 h respectively. Those with advanced HE were offered the option of LT but could not receive LT. SNL in those receiving 4–9 sessions of TPE between 96 h and 28 days was 6/17, 33% at 90 days.

Discussion

The present study has found that after exclusion of cases with advanced HE, TPE is independently associated with improvement in SNL at 90 days in WD with INR ≥ 2.5 and NWI ≥ 11. This difference was significant (67% vs. 41% $p=0.03$) between the TPE group versus no-TPE group. Hence, TPE is associated with 25% more SNL by 90 days in WD with NWI ≥ 11 if cases have no to early HE. More than 3 sessions of TPE (between 96 h and 28 days) also

helped in SNL in one-third (6/17) of the cases who did not improve with 3 sessions of TPE. As reported from South India, mortality without TPE in children with WD and acute liver failure (as per PALF study group) is 54%, including 81.5% with encephalopathy and 32.4% without encephalopathy [10]. Also SNL after TPE has been reported from across the globe: in 6 of 7 fulminant WD Chinese children [11], 2 of the 4 Japanese children [12], an Indian girl [13], and another Turkish girl child [14]. The remaining two Japanese children were successfully transplanted [12]. The Indian girl could not be transplanted and died 8 days after stopping plasma exchange [13]. Another study has reported association of TPE with SNL in 46% of the waitlisted WD patients with NWI ≥ 11 [15]. Two recent studies report transplant-free survival rates of 47% and 85% in 19 and 11 cases of WD from India and China respectively [3, 16]. As is seen in the present study, an earlier report from this same center has shown that the survival benefit with TPE was evident in the subgroup of patients with early HE [3]. A study using database from National Institutes of Health-funded Acute Liver failure Study Group registry has also reported transplant-free survival in those with acute liver injury due to WD, with INR > 2 and no-HE [17].

As evident from Table 2, TPE group showed significant improvement in the INR, albumin, and NWI at 96 h (24 h after the 3rd TPE) in the present study. While this could reflect physiologic improvement, and also that decreased INR and increased albumin levels could reflect replenishment of these liver-derived proteins from blood donors. It is likely to be reversal of liver synthetic dysfunction as this improvement persisted beyond 96 h and associated with improved SNL. The plasma replacement will not show improvement in bilirubin and hence the results are explained well. Albeit not statistically significant, but longer hospital stay was seen in the TPE group versus no-TPE group. Successful bridging to LT was seen in comparable proportions: 6/22 (27.7%) in TPE group as against 9/31 (29%) cases in no-TPE group. Bridging to SNL was seen in statistically comparable proportions in the TPE group (54%) versus no-TPE group (35%). Successful bridging to SNL was seen in statistically ($p = 0.033$) higher proportions in the TPE group (67%) versus no-TPE group (41%) in those with no to early HE. 16 cases of the TPE group who died did not have the option of LT (either because of logistic constraints or due to lack of donor) or refused LT.

In the present study, logistic regression analysis shows that in Model 1, lower INR and TPE at enrollment were found to be independently associated with SNL which can be interpreted as decrease in INR by 1 at enrollment can increase SNL by almost 50% and the use of TPE for the patient can increase the SNL chance by threefold. Another study reports that in patients with fulminant WD, the episode of severe hepatic encephalopathy indicates worse prognosis, and INR is a recommendable predictor. An emergent liver transplantation should be considered for patients whose high INR/prothrombin time below 20%, or for those with severe HE [18]. NWI ≥ 11 not being efficient in independently indicating SNL or poor outcome could be due to the low weightage given to INR in NWI. This was more important at enrollment when the INR was higher. In Model 2, lower NWI (adjusted OR 0.686, 95%CI 0.53–0.89, $p = 0.005$) at 96 h was found to be independently associated with SNL. Hence, decrease in NWI by 1 at 96 h can increase the SNL by 32%.

Initiation of chelation therapy is mandatory in all cases of hepatic WD, but medical therapy cannot remove copper rapidly. Rapid removal of free copper through TPE can benefit WD with liver failure. TPE efficiently removes both ceruloplasmin-bound and albumin-bound copper and the fresh frozen plasma used for exchange can be helpful in treating the associated coagulopathy. TPE can be beneficial to rapidly remove significant amounts of copper from the circulation, an average of 20 mg per TPE treatment. Decreased serum copper may decrease hemolysis, prevent progression of kidney failure, and provide clinical stabilization. TPE can also remove large molecular weight toxins (aromatic amino acids, ammonia, endotoxins) and other factors, which may be responsible for hepatic coma [4]. Molecular Absorption Recirculating System (MARS) is another system, which is able to decrease the serum copper, bilirubin, and creatinine levels by > 25% [19] but all children after MARS subsequently underwent LT. Hence, the recommendations are to use these modalities (TPE/MARS) as bridging therapies to LT. These therapies can be used even in places or cases where LT is not possible.

The limitation of this study is the single-center design. TPE could not be assessed in the advanced disease cases as they were immediately transplanted or died. Since only 63/96 patients were genetically proven, so influence of genotype on outcome could not be studied. Another limitation is the small sample size of the subgroup who received more than 3 sessions and hence could not be analyzed further. To the best of our knowledge, this is the largest cohort of WD with liver failure reported till date. Propensity matched controls strengthen the comparative study. The present study is also different from the rest of the studies as we used combination therapy (both chelators and zinc) for the treatment of WD [20, 21].

Albiet limited, but there are now a series to show that WD with liver failure can have survival with native liver with copper removing therapies. Any chance of survival without LT should be explored to avoid lifelong immunosuppressives and risk for donor in living donor-related LT program. Hepatocyte transplantation has proven safety and efficacy in different acute liver failure etiologies, but the same remains to be demonstrated in WD [22]. So till such

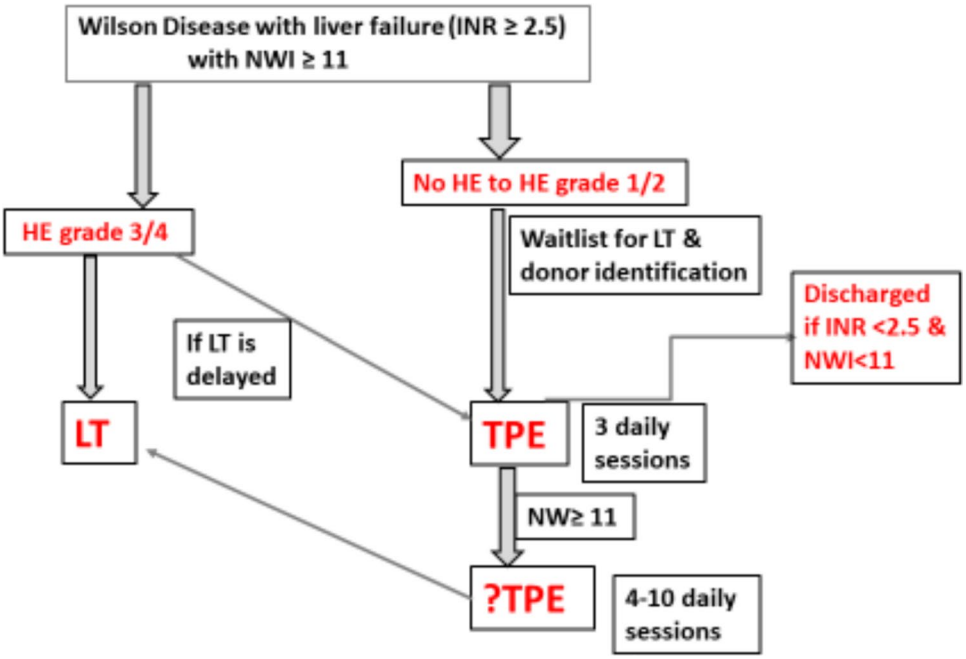


Fig. 3 Algorithmic approach to a Wilson disease with NWI ≥ 11. NWI = New Wilson index, LT = Liver transplant, TPE = Therapeutic Plasma Exchange, HE = Hepatic Encephalopathy

time that hepatocyte transplantation shows efficacy in WD, TPE can be a safe and effective therapy for bridging to SNL. We conclude with an algorithmic approach to WD with liver failure & NWI ≥ 11 (Fig. 3). Since advanced HE is strongly associated with poor outcome, WD cases with advanced HE should be offered immediate LT. For all patients of WD with no to early HE with INR ≥ 2.5 & NWI ≥ 11, waitlisting the child for LT (for donor selection) but 3 daily sessions of TPE should be performed which can improve the SNL by threefold. At the end of 3 sessions, WD with NWI < 11 can be discharged from hospital. Further sessions of TPE in these patients are indicated to maintain NWI < 11 which can increase SNL by 32%.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Snigdha Verma, Seema Alam, Bikrant Bihari lal, Tamoghna Biswas, Vikrant Sood, Rajeev Khanna, Meenu Bajpai declare no financial or non-financial conflict of interest.

Ethical approval The study protocol was approved by the Institutional Ethics Committee of Institute of Liver and Biliary Sciences, New Delhi, India.

Informed consent Informed consent of the patients about the study could not be taken for this study as this was retrospective analysis of preospectively kept data. The study protocol was passed by the institutional review board. Informed consent of every child and family was taken for the TPE.

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