

ORIGINAL ARTICLE

Retrospective analysis of long-term outcome 10 years after liver transplantation for Wilson disease: experience over three decades

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SUMMARY

We evaluated long-term outcomes for patients with Wilson disease (WD) after liver transplantation (LT) and searched for risk factors for poor survival. Retrospective analysis of UNOS/OPTN data identified 156 pediatric and 515 adult cases of LT for WD between 1987 and 2016. Comparison cases were 10 442 pediatric and 104 874 adult non-WD transplant recipients. Survival was calculated using Kaplan–Meier analysis. Recipient, donor, and surgical variables were compared by Cox regression. Survival rates 3, 5, and 10 years after LT for adult WD patients (87.5%, 85.4%, and 80.5%, respectively) were significantly higher than those for non-WD patients ($P < 0.001$); survival rates for pediatric WD patients (90.5%, 89.7%, and 86.5%, respectively) did not differ significantly from non-WD patients. Graft survival in adult and pediatric patients followed similar trends. Regression analysis identified older age, female gender, and use of life support at the time of transplant as risk factors for decreased survival for adults with WD, and younger age, male gender, obesity, and high serum creatinine at the time of transplant as risk factors for poor survival in pediatric recipients with WD. Presentation with fulminant liver failure was not associated with survival in WD patients. No donor characteristic predicted poor survival. Long-term patient and graft survival after LT is excellent for both adult and pediatric WD patients.

Transplant International 2020; 33: 925–935

Key words

graft survival, liver transplantation, patient survival, standard transplant analysis and research, United Network for Organ Sharing, Wilson disease

Received: 1 August 2019; Revision requested: 23 August 2019; Accepted: 14 April 2020; Published online: 12 May 2020

Introduction

Wilson disease (WD) is a disorder caused by a mutation of the ATP7B gene that results in inability to excrete copper into bile. Intracellular copper accumulation may present as hepatic or neuropsychiatric disorders [1,2].

The first published indications of liver transplantation (LT) for WD were described in 1984 [3]. Since that time, LT for end-stage or fulminant liver failure

secondary to WD is recognized by many as life-saving therapy [4]. However, there are few data published regarding the long-term follow-up for patients who have undergone LT for WD [5,6]. Our goals were to (i) compare long-term patient and graft survival after LT for patients with WD vs. patients who received LT for other etiologies (non-WD) over the three decades since 1987 and (ii) identify risk factors for poor patient survival after LT for WD.

Patients and methods

Data source

We used the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) Standard Transplant Analysis and Research (STAR) file. The UNOS/OPTN STAR file contains detailed data for every recipient of a deceased-donor or living-donor transplant since 1987 in the United States and Canada including information obtained at the time of registration and transplantation, such as demographics, certain comorbidities, laboratory results, donor and graft characteristics, and follow-up information of all transplant recipients.

We analyzed data for WD and non-WD patients who underwent LT between October 1, 1987, and December 31, 2016. We stratified the data set into three eras, the first era between October 1, 1987, and December 31, 1994; the second era between January 1, 1995, and December 31, 2006; and the third era between January 1, 2007, and December 31, 2016.

The period of 1987–1994 was chosen because it corresponds to era before the widespread use of tacrolimus, which was approved in April 1994 by the US Food and Drug Administration for use as an immunosuppressive agent after LT [7,8]. The period of 1995–2006 was analyzed to collect 10-year survival data, and the period of 2007–2016 was chosen to see whether any improvement in the outcome for WD patients has occurred over the past decade, especially since the advent of model for end-stage liver disease (MELD) score.

Study variables

The data file was initially separated into adult (age ≥ 18 years) and pediatric recipients. On the basis of diagnosis codes, the adult and pediatric recipients were divided into WD or non-WD groups. Patients with WD were further subdivided according to fulminant liver failure for comparison.

Patient and graft survival was assessed for each group using the follow-up time which is recorded in days after LT to an event in UNOS database. A patient event was defined as either patient death or loss to follow-up. A graft event was defined as graft failure. Patient and graft survival times were then converted into years to simplify the data.

Several factors that were previously shown to influence survival after LT were selected for analysis [9,10]; these included recipient age, gender, ethnicity, body

mass index (BMI), presence of diabetes, baseline creatinine, fulminant liver failure, prior history of dialysis, use of life support (e.g., ventilation), type of donor liver (whole or split), MELD, and the pediatric model for end-stage liver disease (PELD) scores at the time of transplant. Serum creatinine was further classified into normal and high values. According to Junge *et al.* [11], normal serum creatinine in adults was defined as serum creatinine < 1.18 mg/dl in males and < 1.02 mg/dl in females. High serum creatinine in adults was defined as creatinine ≥ 1.18 mg/dl in males and ≥ 1.02 mg/dl in females. Normal serum creatinine in pediatrics was defined as serum creatinine < 0.8 mg/dl in children < 3 years old and < 1.0 mg/dl in children ≥ 3 years old [12]. High serum creatinine in pediatrics was defined as serum creatinine ≥ 0.8 mg/dl in children < 3 years old and ≥ 1.0 mg/dl in children ≥ 3 years old. Donor characteristics such as age, gender, race, donor type, BMI, and cold ischemia time were also included in the current analysis. Available data were complete for all variables except for recipient BMI at the time of transplant and dialysis prior to transplant, which were not uniformly recorded for all cases. Moreover, MELD and PELD scores were not available for all patients because it was introduced by UNOS for organ allocation in February 2002 [13].

Study outcomes

Our main goal was to compare overall patient and graft survival rates at 1, 3, 5, and 10 years after LT for adult and pediatric WD vs. non-WD patients. We also assessed patient and graft survival after LT for adult and pediatric WD patients according to the three eras (1987–1994, 1995–2006, and 2007–2016).

Statistical analysis

Recipient, donor, and surgical characteristics were compared between groups at the time of LT using the Fisher exact test or Student *t*-test for continuous variable and chi-square tests for categorical variables. We estimated the BMI-for-age percentile based on the US Centers for Disease Control and Prevention's growth charts for children and teens with and without WD. Obesity in children was defined as ≥ 95 th BMI-for-age percentile. Univariate Cox regression analysis was performed to estimate the crude hazard ratio (HR) and 95% confidence interval (95% CI) for each risk factor. For multivariable analysis, we performed stepwise Cox regression analysis to build the final survival model. Stepwise Cox

regression analysis was performed for patients received LT after April 2002 to include MELD/PELD scores.

Survival curves were generated by the Kaplan–Meier method, and the statistical significance of differences was determined according to Gehan–Wilcoxon signed-rank test [14]. A *P* value of < 0.05 was considered statistically significant. Cox proportional hazard model was used to identify risk factors for poor survival after LT in WD patients. Stata software (Stata Corp, College Station, TX, USA) was used for statistical analysis.

Results

Population characteristics

The WD group included 671 patients (515 adult and 156 pediatric) after exclusion of 193 patients of multi-organ transplantation or re-transplantation to obtain a more homogenous population. The non-WD group included 115 316 patients (104 874 adult and 10 442 pediatric) after exclusion of multi-organ transplantation or re-transplantation.

Adults who received LT for WD were significantly younger, predominantly female, had higher MELD scores, and had lower BMI than non-WD patients. As shown in Table 1, patients with WD were more likely to be on life support at the time of LT (21.9% vs. 7.2%) and require dialysis prior to transplant (12.2% vs. 5.8%). Among donors, age and BMI were also significantly lower in the adult WD group than in adults transplanted for non-WD etiologies (Table 2).

Pediatric WD patients were significantly older, predominantly female, and more frequently white, with higher BMI and higher PELD scores than non-WD pediatric patients. Significantly higher percentages of pediatric WD patients required life support and had fulminant liver failure. History of dialysis prior to transplant was significantly more common in pediatric WD patients (*P* < 0.001). Unlike the adult population, donor age and BMI were significantly greater in pediatric WD patients than in non-WD pediatric patients. Similar to the adult population, most pediatric patients received deceased-donor liver allografts (*P* = 0.003; Table 2).

Life support codes in UNOS data include the use of ventilator and artificial liver. In our study, the majority of WD and non-WD patients who underwent life support measures at the time of transplant received ventilator support. Both adult and pediatric WD patients had significantly higher rates of ventilator use than did non-WD patients.

Risk factors associated with whole-liver allografts in pediatric WD patients

A higher percentage of pediatric patients with WD had received whole-liver transplants (89%) compared with non-WD patients (75%; *P* < 0.001). We observed that increased serum creatinine (mg/dl), obesity, and age (5-year increments) were associated with the decision to transplant whole-liver allograft among LT recipients after controlling for the potential confounding effects of WD, fulminant liver failure, life support, race, and gender. The estimated odds ratios (95% CI) were 1.6 (1.3–2.1), 1.6 (1.2–2.1), and 1.5 (1.4–1.6) for high serum creatinine, obesity, and age (5-year increments), respectively.

Overall survival rates

Post-transplant overall survival rates at 1, 3, 5, and 10 years for adults with WD were significantly higher than survival rates for non-WD adults (Fig. 1a). Among adult patients with WD, we observed 20% reduction in patients' mortality every 10-year increase from 1987 to 2016 (Fig. 2a). The estimated HR (95% CI) was 0.80 (0.79–0.81), *P* < 0.001, after adjusting for age, gender, and race.

Graft survival rates for adults 1, 3, 5, and 10 years after LT for WD were also significantly better than those for non-WD patients (Fig. 1b). Among adult patients with WD, we observed 26% reduction in graft failure with every 10-year increase from 1987 to 2016 (Fig. 2b); the estimated HR (95% CI) was 0.74 (0.55–1.00), *P* = 0.05, after adjusting for age, gender, and race.

Pediatric WD patients had high overall survival rates 1, 3, 5, and 10 years after LT compared with non-WD patients (Fig. 3a). Among pediatric patients with WD, we observed 49% reduction in patients' mortality every 10-year increase from 1987 to 2016 (Fig. 4a). The estimated HR (95% CI) was 0.51 (0.27–0.97), *P* = 0.04, after adjusting for age, gender, and race.

There were no statistically significant differences in graft survivals between WD and non-WD pediatric LT recipients (Fig. 3b). Among pediatric patients with WD, we observed 47% reduction in graft failure with every 10-year increase from 1987 to 2016 (Fig. 4b); the estimated HR (95% CI) was 0.53 (0.28–0.99), *P* = 0.04, after adjusting for age, gender, and race.

Risk factors for poor survival after LT for WD

Multivariable Cox regression analysis showed that older age, female gender, non-white ethnicity, and receipt of life

Table 1. Demographic and clinical characteristics of liver transplant recipients.

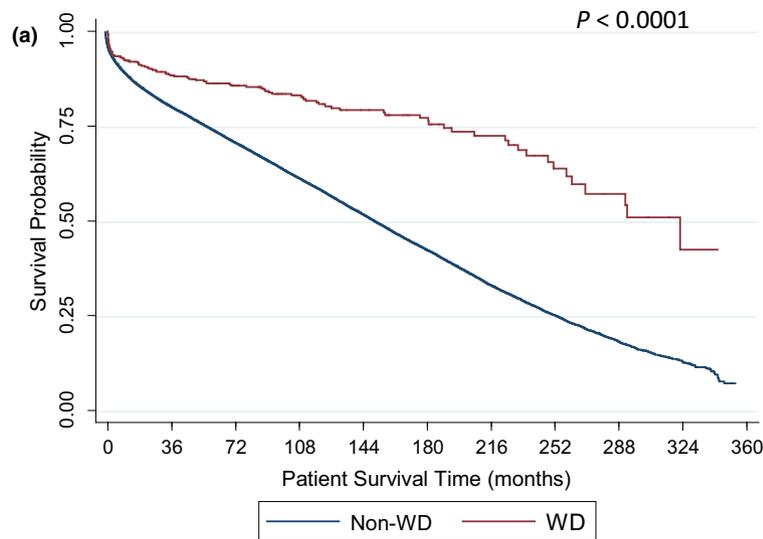
Characteristic	Number (%)		P	Number (%)		P
	Adult recipients			Pediatric recipients		
	WD N = 515	Non-WD N = 104 874		WD N = 156	Non-WD N = 10 442	
Median (IQR) age, years	30 (18–72)	54 (18–84)	<0.001	14 (11–16)	2 (0–8)	<0.001
Gender			<0.001			0.01
Male	248 (48.2)	67 767 (64.6)		60 (38.5)	5102 (48.9)	
Female	267 (51.8)	37 107 (35.4)		96 (61.5)	5304 (51.1)	
Race			0.002			<0.001
White	392 (76.1)	78 378 (74.7)		115 (73.7)	5846 (56.0)	
Black	23 (4.5)	8352 (8.0)		8 (5.1)	1717 (16.4)	
Hispanic	74 (14.4)	12 530 (12.0)		20 (12.8)	2056 (19.7)	
Other	24 (4.7)	5560 (5.3)		13 (8.3)	806 (7.7)	
Unknown	2 (0.4)	54 (0.1)		0	17 (0.2)	
Median (IQR) BMI, kg/m ²	26.0 (15.5–52.9)	27.3 (15.0–72.8)	0.06	20.9 (13.4–33.2)	17.2 (7.3–45.3)	<0.001
Diabetes	16 (3.8)	20 515 (22.2)	<0.001	0	82 (1)	0.3
Median (IQR) serum creatinine, mg/dl	1.1 (0.8–1.8)	1 (0.8–1.5)	0.002	0.8 (0.6–1.5)	0.3 (0.2–0.5)	<0.001
Normal serum creatinine	298 (57.9)	71 962 (68.7)	0.001	106 (67.9)	9954 (95.3)	0.001
High serum creatinine	217 (42.1)	32 912 (31.3)		50 (32.1)	488 (4.7)	
Liver disease status			<0.001			<0.001
Fulminant	181 (35.2)	4274 (4.1)		86 (55.1)	1517 (14.5)	
Chronic	334 (64.8)	100 600 (95.9)		70 (44.9)	8925 (85.5)	
Dialysis prior to LT	63 (12.2)	6130 (5.8)	<0.001	23 (14.7)	245 (2.3)	<0.001
On life support	113 (21.9)	7549 (7.2)	<0.001	32 (20.5)	1276 (12.3)	0.002
On ventilator	101 (19.6)	5815 (5.5)	<0.001	28 (18)	1149 (11)	0.01
Donor liver allograft			0.5			<0.001
Whole-liver allograft	494 (96)	100 016 (95.3)		139 (89)	7816 (75)	
Split-liver allograft	21 (4.0)	4858 (4.6)		17 (11)	2626 (25)	
MELD/PELD score			<0.001			<0.001
≤14	24 (4.6)	22 208 (21.2)		5 (3.2)	2965 (28.4)	
≥15	295 (57.3)	48 784 (46.5)		77 (49.4)	2925 (28.0)	
Unreported	196 (38.1)	33 882 (32.3)		74 (47.4)	4552 (43.6)	

SD, standard deviation; IQR, interquartile range.

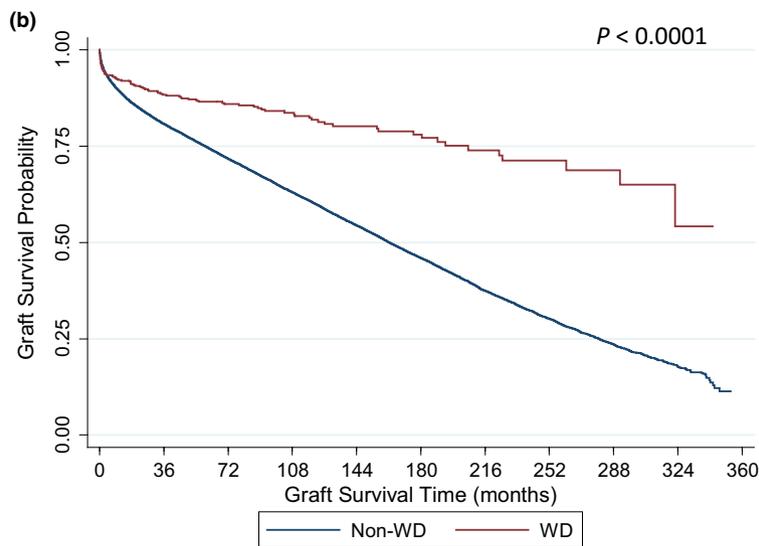
Table 2. Demographics and clinical characteristics of liver donors.

Characteristic	Number (%)		P	Number (%)		P
	Donors for adult patients			Donors for pediatric patients		
	WD N = 515	Non-WD N = 104 874		WD N = 156	Non-WD N = 10 442	
Median (IQR) age, years	32 (3–85)	39 (1–93)	<0.001	21.5 (15.0–37.0)	10 (2–22)	<0.001
Gender			0.09			0.2
Male	292 (56.7)	63 248 (60.3)		95 (60.9)	5886 (56.4)	
Female	223 (43.3)	41 614 (39.7)		61 (39.1)	4554 (43.6)	
Race			0.2			0.08
White	376 (73.0)	74 714 (71.2)		116 (74.4)	6700 (64.2)	
Black	74 (14.4)	14 775 (14.1)		15 (9.6)	1623 (15.5)	
Hispanic	57 (11.1)	11 758 (11.2)		20 (12.8)	1680 (16.1)	
Other	8 (1.6)	3482 (3.3)		4 (2.6)	406 (3.9)	
Unknown	0	145 (0.1)		1 (0.6)	33 (0.3)	
Donor type			0.4			0.003
Deceased	500 (97.1)	101 087 (96.4)		148 (94.9)	9073 (86.9)	
Living	15 (2.9)	3787 (3.6)		8 (5.1)	1369 (13.1)	
Median (IQR) BMI, kg/m ²	24.9 (13.3–65.3)	25.6 (9.2–73.2)	0.003	22.4 (10.7–44.2)	19.5 (7.2–52.2)	<0.001
Mean (± SD) cold ischemia time, hours	7.7 ± 4.4	7.5 ± 4.1	0.3	7.9 ± 3.9	7.9 ± 4.9	0.9

SD, standard deviation; IQR, interquartile range.



	Patient Survival WD (95% CI)	Patient Survival non-WD (95% CI)
1-year	91.2% (88.5–93.5)	87.9% (87.8–88.2)
3-year	87.5% (84.2–90.2)	79.8% (79.6–80.1)
5-year	85.4% (81.2–88.3)	73.7% (73.4–73.9)
10-year	80.5% (75.5–83.8)	58.6% (57.7–58.4)



	Graft Survival WD (95% CI)	Graft Survival non-WD (95% CI)
1-year	91.2% (88.5–93.5)	87.8% (87.8–88.2)
3-year	87.5% (84.2–90.2)	79.9% (79.7–80.2)
5-year	85.7% (82.2–88.6)	74.1% (73.8–74.3)
10-year	81.4% (76.7–84.6)	60.2% (59.3–60.1)

Figure 1 (a) Comparison of overall patient survival after liver transplant in adult Wilson disease (WD) and non-WD patients. (b) Comparison of graft survival after liver transplant in adult WD and non-WD patients.

support were significantly associated with shorter overall survival among adults with WD. For example, women had twice the risk of death than did men after LT (HR = 2.1,

95% CI = 1.1–4.1, $P = 0.03$; Table 3). Among adults with WD, each 10-year increase in age at transplant was associated with 40% increase in post-transplant mortality.

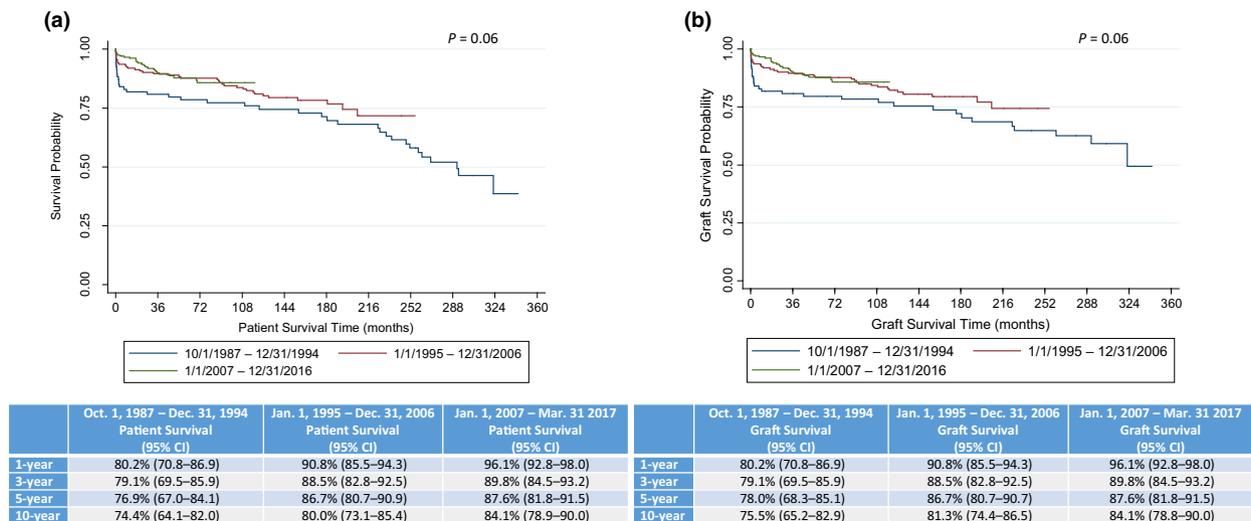


Figure 2 (a) Overall patient survival in adult Wilson disease (WD) patients after liver transplant by era. (b) Graft survival in adult WD patients after liver transplant by era.

Among pediatric patients who received LT for WD, multivariable Cox regression analysis indicated that younger age, male gender, obesity, and high serum creatinine were significant risk factors for shorter overall survival after LT. Obese patients had four times the risk of death compared with normal BMI patients (HR = 4.5, 95% CI = 1.3–15.7, $P = 0.02$).

Transplantation for fulminant liver failure was not a significant risk factor for poor survival in both adult and pediatric age groups. No donor characteristic was identified as a risk factor for poor survival in WD patients after LT in univariate analyses.

Discussion

This study showed that patients with WD have excellent survival rates at 1, 3, 5, and 10 years after LT. Although we do not have scientific explanation for our observation, it is possible that this outcome results from younger age at transplant in adult WD patients, low prevalence of hepatocellular carcinoma pretransplant [15,16], and no recurrence of copper storage in the allograft in the WD group [17]. Furthermore, advances in WD diagnosis by molecular testing [1,18] and functional neuroimaging [19] in patients presented with nonspecific symptoms, and improvement in immunosuppression [20] contributed to the improved yet non-significant trend in overall patient survival after LT for patients with WD over the past three decades.

We believe our study is the first to report long-term outcomes (10 years) for WD patients after LT in the

United States. It showed that LT for WD was performed at younger age in adults, older age in children, and more often in females compared with LT for non-WD indications, for whom demographics were similar to previously published data [5]. Both European and US reported data [5,21] showed the predominance of female gender among patients with WD undergoing LT, and this predominance was attributed to hormonal influence, especially in fulminant liver failure because of WD [22,23]. Female gender has been associated with an increased risk of death or being too sick for transplant listing [5,6].

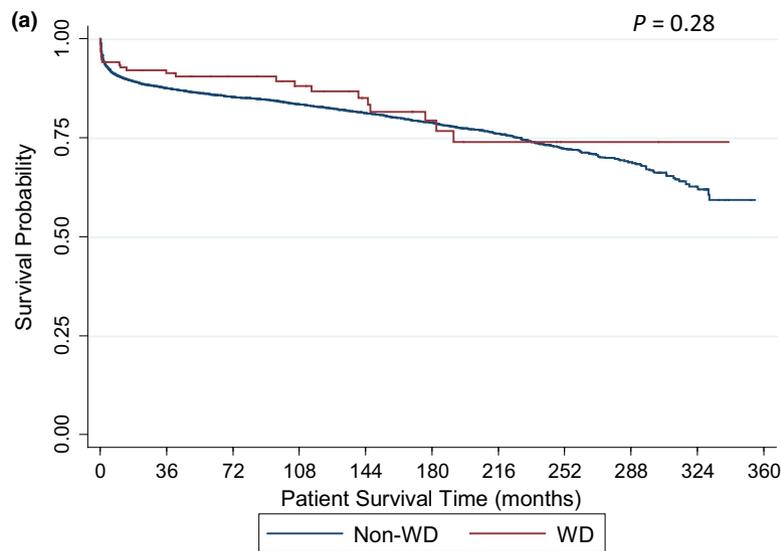
In our study, old age, female gender, non-white ethnicity, and use of life support at the time of transplant were identified as risk factors for death in adult patients with WD after LT. These factors were not identified in a previous study using the same database between 2002 and 2008 [5]. We believe that such discrepancy occurred because they studied a shorter period. Likewise, a French study [6] reported no medically relevant risk factors for poor prognosis among 75 adult WD patients after LT, possibly because of sample size.

Pediatric WD patients received whole-liver transplants at a significantly higher rate compared with non-WD patients. Our results supported the impact of higher serum creatinine levels, obesity, and older age as risk factors for whole-liver transplantation in the pediatric WD group. However, the use of whole- or split-liver graft was not a risk factor for poor survival in pediatric WD group.

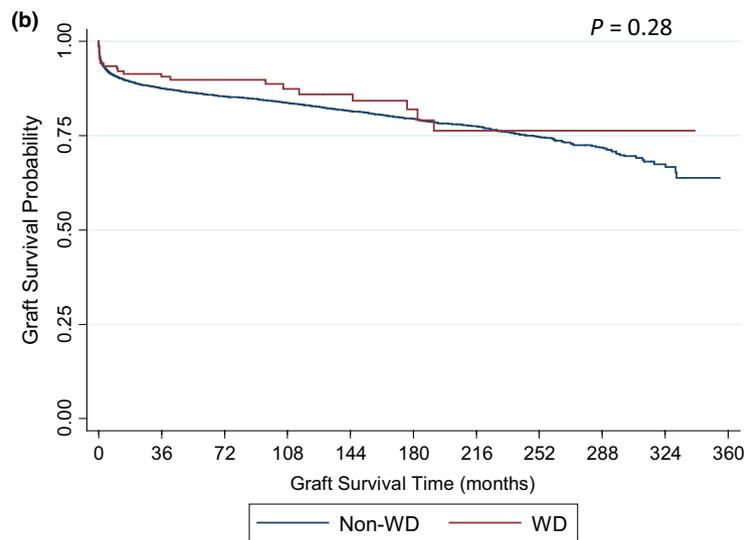
Table 3. Recipient characteristics as predictors of survival after LT in WD patients.

Characteristic	Adult WD recipients (N = 515)			Pediatric WD recipients (N = 156)					
	Univariate analysis		Multivariate analysis	Univariate analysis		Multivariate analysis			
	HR (95% CI)	P	HR (95% CI)	HR (95% CI)	P	HR (95% CI)	P		
Age (10 years)	1.02 (1.01–1.04)	0.001	1.4 (1.1–1.8)	0.004	Age (5 years)	0.93 (0.82–1.06)	0.3	0.36 (0.16–0.84)	0.02
Female gender	1.49 (1.00–2.20)	0.04	2.1 (1.1–4.1)	0.03		0.33 (0.11–0.97)	0.04	0.27 (0.7–1.0)	0.05
Non-white race	1.4 (0.93–2.18)	0.1	1.3 (1.1–1.7)	0.02		1.00 (0.39–2.55)	0.9		
BMI < 25 kg/m ²	1				Normal/slim	1			
BMI 25–<30 kg/m ²	0.98 (0.62–1.55)	0.9			Overweight	2.32 (0.89–6.02)	0.08	2.60 (0.87–7.80)	0.9
BMI ≥ 30 kg/m ²	0.96 (0.57–1.59)	0.8			Obese	4.28 (1.31–13.9)	0.01	4.5 (1.3–15.7)	0.02
Creatinine (mg/dl)	1.11 (0.99–1.24)	0.07				1.23 (1.05–1.45)	0.01	1.18 (0.98–1.41)	0.08
On life support	1.92 (1.27–2.90)	0.002	2.9 (1.5–5.8)	0.002		2.60 (1.13–5.96)	0.02		
On ventilator	1.80 (1.17–2.75)	0.007	-	-		1.99 (0.83–4.73)	0.1		
Fulminant liver failure	0.86 (0.56–1.32)	0.5				1.06 (0.46–2.43)	0.9		
Whole-liver allograft	0.82 (0.30–2.24)	0.7			PELD score*	0.99 (0.23–4.26)	0.9		
MELD score*	1.18 (0.36–3.82)	0.7				0.33 (0.03–2.85)	0.3		

*Stepwise Cox regression analysis was performed for patients received LT after April 2002 to include MELD/PELD scores.



	Patient Survival WD (95% CI)	Patient Survival non-WD (95% CI)
1-year	92.0% (86.6–95.5)	89.5% (88.9–90.1)
3-year	90.5% (84.8–94.4)	86.9% (86.3–87.6)
5-year	89.7% (83.8–93.8)	85.4% (84.8–86.2)
10-year	86.5% (78.5–91.3)	82.3% (81.5–83.1)



	Graft Survival WD (95% CI)	Graft Survival non-WD (95% CI)
1-year	91.3% (85.8–94.9)	89.5% (89.0–90.2)
3-year	89.9% (84.0–93.9)	86.8% (86.3–87.6)
5-year	89.1% (83.1–93.3)	85.2% (84.7–86.1)
10-year	85.9% (77.7–90.7)	82.4% (81.6–83.2)

Figure 3 (a) Comparison of overall patient survival after liver transplant in pediatric Wilson disease (WD) and non-WD patients. (b) Comparison of graft survival after liver transplant in pediatric WD and non-WD patients.

On multivariable analysis of the pediatric WD group in our study, reason for LT (fulminant vs. chronic WD), and gender of the donor had no significant

effect on patient survival and were similar to the European data [21]. Overall patient and graft survival in our pediatric WD group was higher compared with

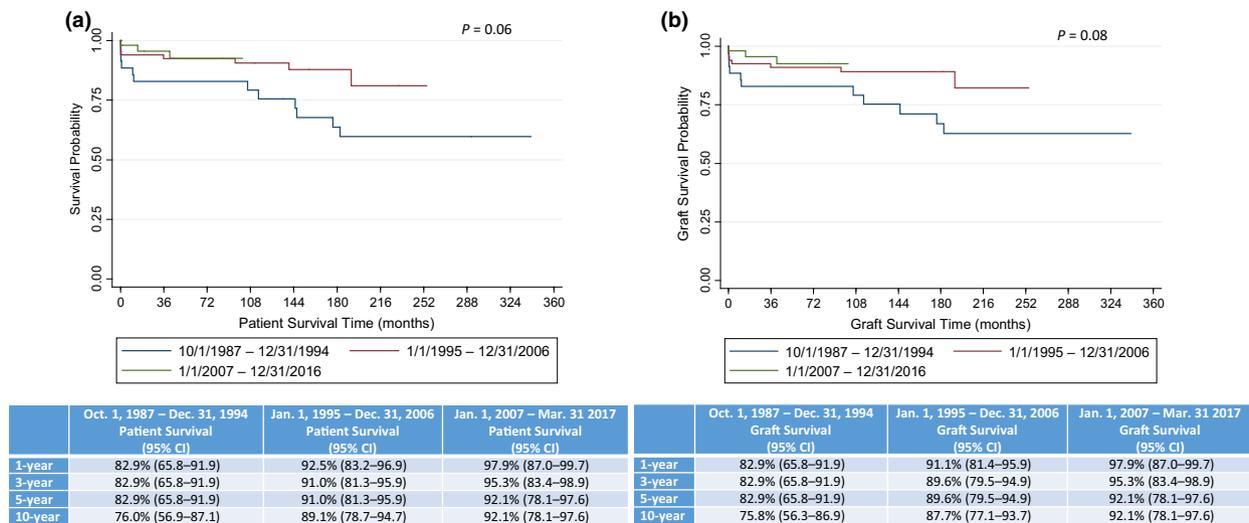


Figure 4 (a) Overall patient survival in pediatric Wilson disease (WD) patients after liver transplant by era. (b) Graft survival in pediatric WD patients after liver transplant by era.

the reported European data at 1, 5, and 10 years after LT [21].

It is notable that survival in European pediatric WD patients increased considerably over three decades, from a 1-year survival rate of 50% in the 1980s to a 93% rate after 2010 [21]. On the other hand, 1-year patient survival in the US data was 82.9% in the 1980s and 97.9% after 2007. This difference may be related to demographic variation in presentation or patient selection criteria and warrants further study.

Overall 5-year patient survival is as low as 67% after LT for fulminant liver failure in the literature [24,25]. This low survival rate is generally believed to be related to complications occurring early after LT secondary to the initial presentation with multi-organ failure. On the other side, 5-year patient survival after LT for fulminant WD was 85.9% in our study, which was substantially better than the rate for patients who underwent LT for fulminant liver failure of different etiologies. Better survival outcomes for patients with fulminant WD after LT are most likely because of no recurrence of disease after LT compared to patients with fulminant non-WD.

Our study has limitations associated with the retrospective nature of a large database analysis. The results regarding survival and factors affecting survival rely entirely on the accuracy of recorded data gathered in the UNOS database. MELD scores were not available prior to February 2002, which meant that patients who underwent LT for WD from 1987 to 2002 did not have MELD scores and were not included in our regression analysis. Also, this study only evaluated patients who

underwent LT for WD and non-WD indications, and therefore did not include any information regarding transplant-free survival in patients with WD who were on the waitlist or had stable disease and were receiving therapy. Finally, UNOS STAR files do not contain information regarding neurologic status before or after LT, and these files lack information about neurological recovery after LT. Therefore, the current results can only be applied to WD patients experiencing hepatic failure.

In conclusion, patients who undergone LT for end-stage or fulminant liver failure secondary to WD have excellent long-term survival outcomes. LT for end-stage or fulminant liver failure secondary to WD should be considered an excellent therapy for long-term patient and graft survival, both in adults and in pediatrics. Outcomes after LT were comparable between fulminant and chronic presentations of WD. Non-white patients and older women are at high risk of suboptimal outcomes in the long term. Future studies are needed to understand the mechanisms underlying these disparities. In the interim, our results suggest that these subgroups should be monitored carefully following LT for WD.

Authorship

All authors approved the final version of the manuscript.

MSI and AM-C: conceived and designed the study, acquired the data, and drafted the manuscript. MH: designed the study, involved in statistical analysis, and drafted the manuscript. SM: designed the study and involved in statistical analysis. PKJ: conceived and

designed the study. All authors interpreted the data and critically revised the manuscript.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflicts of interest.

Acknowledgments

We thank Scientific Publication Department, MD Anderson Cancer Center, Houston, TX, for their editing support.

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