Title

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Journal

Liver Transplantation, 12(9)

ISSN

1527-6465

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Publication Date

2006-09-01

DOI

10.1002/lt.20806

ORIGINAL ARTICLE

Predictors of Clinical Outcome in Children Undergoing Orthotopic Liver Transplantation for Acute and Chronic Liver Disease

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The current United Network for Organ Sharing (UNOS) policy is to allocate liver grafts to pediatric patients with chronic liver disease based on the pediatric end-stage liver disease (PELD) scoring system, while children with fulminant hepatic failure may be urgently listed as Status 1a. The objective of this study was to identify pre-transplant variables that influence patient and graft survival in those children undergoing LTx (liver transplantion) for FHF (fulminant hepatic failure) compared to those patients transplanted for extrahepatic biliary atresia (EHBA), a chronic form of liver disease. The UNOS Liver Transplant Registry was examined for pediatric liver transplants performed for FHF and EHBA from 1987 to 2002. Variables that influenced patient and graft survival were assessed using univariate and multivariate analysis. Kaplan-Meier analysis of FHF and EHBA groups revealed that 5 year patient and graft survival were both significantly worse ($P < 0.0001$) in those patients who underwent transplantation for FHF. Multivariate analysis of 29 variables subsequently revealed distinct sets of factors that influenced patient and graft survival for both FHF and EHBA. These results confirm that separate prioritizing systems for LTx are needed for children with chronic liver disease and FHF; additionally, our findings illustrate that there are unique sets of variables which predict survival following LTx for these two groups. ***Liver Transpl 12:1347-1356, 2006.***

Received August 24, 2005; accepted March 16, 2006.

Fulminant hepatic failure (FHF) is a poorly understood disorder defined as severe liver injury in the absence of preexisting liver disease with the onset of encephalopathy in less than 8 weeks after symptoms have begun.[1] In children, it is a rare but often times fatal disorder that is secondary to a variety of causes including infection, toxin or drug-induced injury, and a variety of metabolic diseases. In contrast to the adult population, the cause of FHF in children in the United States often is of unknown etiology.[2] Together, these may account for as many as 50% of cases. In the absence of liver transplantation (LTx), FHF of indeterminate etiology is associated with a poor clinical prognosis with a fatality rate as high as 90%.[3] The treatment of FHF is primarily supportive, and may require LTx if there are no signs of recovery. Only a small fraction of patients with FHF spontaneously regain normal function, meaning that the majority of patients who do survive undergo LTx. Unfortunately, pediatric LTx is limited by both the scarcity of available donors and by the development of irreversible complications associated with liver failure that make LTx contraindicated. Since most cases of FHF require LTx within a period of days to weeks after the onset of liver disease, clinicians must decide in a timely manner when to list a child for transplantation before his or her clinical condition deteriorates.

In contrast to the acute nature of FHF, extrahepatic biliary atresia (EHBA) often leads to chronic end-stage liver disease, and is the most common cause of pediatric LTx. Children with EHBA generally present in early infancy with cholestasis and, if diagnosed in a timely manner, often undergo Kasai portoenterostomy during the first several months of life. Despite early surgical intervention, more than half of the infants with EHBA

Abbreviations: FHF, fulminant hepatic failure; LTx, liver transplantation; EHBA, extrahepatic biliary atresia; UNOS, United Network for Organ Sharing; PELD, pediatric end-stage liver disease.

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DOI 10.1002/lt.20806
Published online in Wiley InterScience (www.interscience.wiley.com).

progress over a period of months to years to end-stage liver disease ultimately requiring LTx.[4-6]

In the past, regardless of etiology, the diagnosis of end-stage liver disease in children, whether acute or chronic, carried a poor prognosis. With the advent of LTx, as well as advances in surgical techniques, immunosuppresion and post-transplant medical care, the 5 year survival rate has improved to greater than 80%.[3]

The current United Network for Organ Sharing (UNOS) policy is to allocate liver grafts to pediatric patients with chronic liver disease based on the pediatric end-stage liver disease (PELD) scoring system.[7] This system was implemented in 2002, and it uses important patient clinical characteristics such as bilirubin, international normalized ratio, albumin, growth failure, and age at transplant in order to allocate donor livers. The premise behind the PELD system is to predict a child's risk of dying while awaiting LTx, and to allocate organs to patients with the greatest need. While this scoring system clearly pioneers the distribution of donor livers with the use of evidence-based data, it is limited to children with chronic liver disease, and does not include specifics for those with FHF. There are no evidence-based methods currently in place to facilitate the distribution of livers to children with FHF. Instead, the decision of whether or not to transplant these patients is currently based primarily on the clinical progression of their disease. Once children with FHF are listed for LTx, they will now fall under the new status 1a category, which requires them to have the onset of hepatic encephalopathy within 8 weeks of their first symptoms, be in a pediatric ICU, and have one or more of the following: ventilator dependence, dialysis/continuous venovenous hemofiltration or continuous venovenous hemofiltration with dialysis, or INR $>$ 2.0. Given the short supply of available organs, developing a ranking system which prioritizes children with acute failure that are not only in greatest need of a transplant, but who are also most likely to survive surgery needs to be established. Therefore, the objective of this study was to identify pre-transplant variables that influence patient and graft survival in those children undergoing LTx for FHF and EHBA. We hypothesized that due to the distinct features of FHF and EHBA, the list of cofactors which predict outcomes in these two groups would be quite different.

METHODS

A retrospective review of the UNOS nationwide database was performed. The initial database contained 53,833 transplantations that occurred between October 1987 and May 2002 in the United States. 7,894 of these transplants were performed in recipients 18 years of age or less; 3,013 carried the diagnosis of either FHF or EHBA. Retransplants (283 patients) were excluded from analysis, leaving 2,730 pediatric patients who underwent primary LTx for FHF or EHBA. Of these 2,730 patients included, 932 were transplanted for FHF and 1,798 for EHBA (Figure 1). Within the 932 patients with FHF, 666 patients (72%) were diagnosed with FHF of unknown etiology, 110 (12%) had a known viral hepatitis, 56 (6%) had acetaminophen-induced hepatic failure, 35 (4%) had FHF secondary to a drug other than acetaminophen, and the remaining 60 (6%) patients had a metabolic or other diagnosis as the cause of their FHF. As mentioned, subjects were identified in the UNOS database with the diagnosis of EHBA by the code 4270.

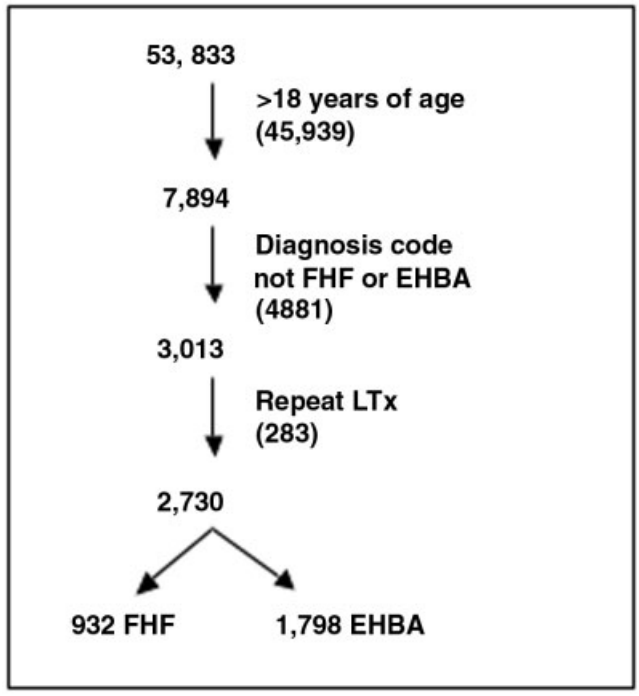

Figure 1. The exclusion criteria for patients from the original UNOS database of liver transplants.

While the entire UNOS dataset contained more than 380 variables, we selected 29 potential peri-transplant covariates (Figure 2). Based on literature in this field and experience at a major pediatric transplant center, these cofactors were believed to be relevant in possibly affecting clinical outcome and reflecting the degree of liver disease. The variables can be classified into three categories: 1) recipient variables (including epidemiologic information, pre-transplant clinical condition, and pre-transplant laboratory values), 2) donor variables, and 3) operative variables.

In this analysis, recipient status codes (alive, dead, retransplanted and lost to follow-up) were assigned as primary outcomes, and the follow-up days after the LTx was used to determine the time-dependency of the clinical outcome.

Statistical Analysis

The final outcomes assessed were 5-year patient and graft survival. All analyses were carried out separately on FHF and EHBA patients using Kaplan-Meier methods. Univariate analysis was carried out on all 29 variables. Variables with a continuous scale were analyzed by quartiles and variables with skewed distributions were normalized using log transformation. Death and graft failure rates as well as the hazard ratios were calculated for each subcategory. Whenever possible,

Recipient variables

1. Age
2. Gender
3. Ethicity
4. UNOS region where transplanted
5. ABO type
6. Time on waiting list
7. Initial waiting list status code
8. Status code at time of transplant
9. More than one transplant
10. Medical condition at registration
11. Medical condition at transplant
12. Grade 3, 4 encephalophy at registration
13. Grade 3, 4 encephalophy at transplant
14. Life support at registration
15. Life support at transplant
16. Ventilator at registration
17. Ventilator at transplant
18. Serum albumin at transplant
19. Serum alkalin phosphatase at transplant
20. Serum billrubin at transplant
21. Serum AST at transplant
22. Serum ALT at transplant
23. Serum prothrombin time at transplant
24. Serum creatinine at transplant

Donor variables

25. Donor age
26. Blood type mismatch
27. Distance of donor

Operative variables

28. type of live graft
29. Cold ischemic time

Figure 2. List of UNOS variables

subcategories were grouped together when their death or failure rates were similar and when the grouping was clinically logical. This was done in order to simplify the number of subcategories and increase statistical power for multivariate analysis. Univariate tests of significance were carried out using the log rank tests. All*P*-values reported are two-sided. Those variables found to be significant ($P < 0.05$) or approaching significance (defined as $P < 0.20$) at the univariate level were then included as candidates for a multivariate model along with any variables deemed clinically important, whether they were statistically significant or not.

The multivariate analyses were performed using Cox proportional hazard models for time to patient and graft loss. When two statistically significant predictors strongly correlated with each other (proxies) and were both clinically relevant, the one with the fewer missing values was selected as a candidate for the final model. Due to different patterns of missing data, the number of patients for analysis varied. Furthermore, different model groups were evaluated by including or excluding those variables with missing values. Specifically, we compared the state versus region in the analysis of the FHF group and compared the EHBA analysis with and without bilirubin data. Missing data for other variables included in the models were negligible and were excluded.

RESULTS

Kaplan-Meier Analysis

Curves for patient and graft survival for the FHF and EHBA groups are shown in Figure 3. Five year patient survival after transplantation was 89% in the EHBA group vs. 73% in the FHF group ($P < 0.0001$); five year graft survival was 78% (EHBA) and 59% (FHF) respectively ($P < 0.001$).

Univariate Analysis

FHF group

Ten of the initial 29 variables examined, in univariate analysis proved to be statistically significant ($P < 0.05$) in influencing FHF patient survival post-transplant. All of these variables were related to the recipient; they are listed in Table 1A and marked with[1].

Six additional variables that approached significance ($P < 0.20$) were retained for the multivariate model including: the state of residence, the UNOS region where the patient was transplanted, initial waiting list status code, serum creatinine at transplant, donor age, and the distance from the donor hospital to the transplant center.

All of the variables that were significant in graft survival are listed in Table 1A and labeled with [2]. The same variables which affected patient survival post-transplant also proved to be significant for graft survival with the exception of three variables (the recipient age, ventilator dependence at time of registration, and presence of encephalopathy at time of transplant) which all only approached significance. Furthermore, four additional variables including the patient's serum creatinine and alkaline phosphatase at transplant, the age of the donor, and the distance of the donor from the transplant center were found to be significant in influencing graft survival in the FHF group.

For graft survival, an additional 10 variables that approached significance ($P < 0.20$) were retained as candidates for the corresponding multivariate model. These variables included recipient age, ventilator dependence at time of registration, presence of encepha-

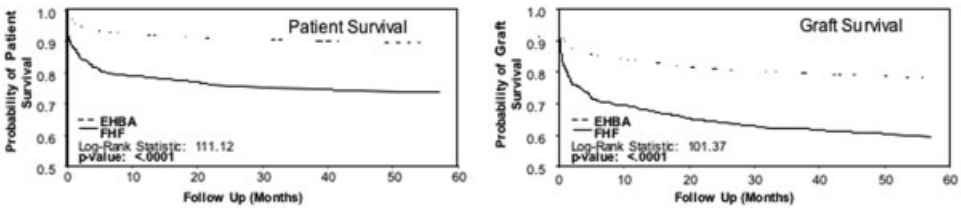

Figure 3. Kaplan-Meier analysis of patient and graft survival over a 5-year period. Compared to the EHBA patients, long term patient and graft survival is significantly worse in those who underwent transplantation for FHF.

TABLE 1A. Univariate Analysis Demonstrating Significant Variables in the FHF Group

Fulminant Hepatic Failure							
		Patient Survival			Graft Survival		
Variable	Variable category	Death rate*	Death rate ratio	p-value	Graft failure	Graft failure rate ratio	p-value
Age of recipient (years) 1	Age < = 2	10.313	1.000	0.008	1.401	1.000	0.0832
	2 < Age < = 7	6.716	0.651		1.036	0.740	
	7 < Age < = 14	4.431	0.430		0.840	0.599	
	Age > 14	7.123	0.691		1.250	0.892	
Grade 3, 4 encephalopathy at transplant 1	Yes	10.206	1.000	0.017	1.436	1.000	0.0775
	No	6.096	0.597		1.084	0.755	
Ventilator at registration 1	Yes	14.052	1.000	0.037	1.905	1.000	0.1640
	No	6.065	0.432		1.010	0.530	
Ventilator at transplant 1, 2	Yes	10.967	1.000	<.0001	1.558	1.000	<.0001
	No	4.508	0.411		0.868	0.557	
Life support at registration 1, 2	Yes	14.052	1.000	0.037	1.905	1.000	<.0001
	No	6.065	0.432		1.010	0.530	
Life support at transplant 1, 2	Yes	10.927	1.000	<.0001	1.563	1.000	<.0001
	No	3.575	0.327		0.721	0.461	
Medical condition at registration 1, 2	Requiring ICU care	8.655	1.000	0.003	1.310	1.000	0.0246
	Hospitalized, but not in ICU	6.716	0.776		1.023	0.781	
	Not hospitalized	3.446	0.398		0.875	0.668	
Medical condition at transplant 1, 2	Requiring ICU care	8.208	1.000	<.0001	1.225	1.000	0.0033
	Not requiring ICU care	2.943	0.359		0.743	0.606	
Blood type mismatch 1, 2	Yes	12.42	1.000	0.0001	1.866	1.000	<.0001
	No	6.477	0.512		1.046	0.560	
More than one transplant 1, 2	Yes	2.423	1.000	0.0003	12.601	1.000	<.0001
	No	7.193	2.968		0.830	0.066	
Donor age (years) 2	Donor age < = 7	5.651	1.000	0.137	0.884	1.000	0.01
	7 < Donor age < = 34	6.545	1.158		1.040	1.176	
	Donor age > 34	11.189	1.980		1.797	2.033	
Serum creatinine at transplant 2	log creat < = −0.523	8.698	1.000	0.107	1.256	1.000	0.015
	(−)0.523 < log creat < −0.09	5.672	0.652		0.937	0.746	
	log creat > −0.097	9.400	1.081		1.482	1.180	
Distance of donor hospital to transplant center (miles) 2	distance < = 29	6.979	1.000	0.120	1.115	1.000	0.039
	29 < distance < = 588	6.752	0.967		1.082	0.953	
	distance > 588	7.771	1.113		1.243	1.116	
Serum alkaline phosphatase at transplant 2	log alk < = 2.361	6.576	1.000	0.265	1.058	1.000	0.028
	log alk > 2.361	16.082	2.446		2.297	2.172	

*Death rate and graft failure rate (listed per 1,000 person months of follow-up)
1 = Significant variable in patient survival ($P < 0.05$)
2 = Significant variable in graft survival ($P < 0.05$)

lopathy at time of transplant, ethnicity, state of residence, initial waiting list status code, status code at time of transplant, time on waiting list, serum albumin at transplant, and organ donor type.

EHBA group

Within the EHBA group, we could fairly evaluate only 18 of the 29 variables since the remaining 11 variables had too few patients or too many missing values. For

TABLE 1B. Univariate Analysis Demonstrating Significant Variables in the EHBA Group

Extrahepatic Biliary Atresia							
		Patient Survival			Graft Survival		
Variable	Variable category	Death rate*	Death rate ratio	p-value	Graft failure	Graft failure rate ratio	p-value
Medical condition at registration 2	Requiring ICU care	2.117	1.000	0.2859	0.645	1.000	<.0001
	Not requiring ICU care	2.028	0.958		0.420	0.651	
Medical condition at transplant 1, 2	Requiring ICU care	3.118	1.000	0.0005	0.638	1.000	<.0001
	Not requiring ICU care	1.801	0.578		0.403	0.632	
Ventilator at registration 1, 2	Yes	10.749	1.000	0.0002	3.822	1.000	<.0001
	No	1.922	0.179		0.410	0.107	
Donor age (years) 1, 2	Age < = 6	1.427	1.000	0.0078	0.373	1.000	0.0030
	Age > 6	2.856	2.001		0.543	1.456	
Liver organ type 1, 2	Whole graft	1.405	1.000	<.0001	0.321	1.000	<.0001
	Split graft	3.729	2.653		0.790	2.461	
Serum creatinine at transplant 1	log creat < = −0.699	0.937	1.000	0.0057	0.296	1.000	0.2297
	log creat > −0.699	2.205	2.353		0.469	1.587	
Ethnicity 1	White	1.823	1.000	0.0209	0.404	1.000	0.606
	Black	2.551	1.400		0.500	1.237	
	Hispanic	1.367	0.750		0.478	1.184	
	Asian	3.017	1.655		0.503	1.244	
UNOS region where transplanted 1, 2	1, 6, 11	5.185	1.000	0.0036	0.767	1.000	0.0029
	2	0.916	0.177		0.260	0.339	
	3, 4	2.943	0.568		0.632	0.823	
	5	1.996	0.385		0.408	0.531	
	7, 8	1.766	0.341		0.442	0.576	
	9, 10	2.314	0.446		0.481	0.627	
Serum albumin at transplant 2	log alb < = 0.431	2.579	1.000	0.2960	0.555	1.000	0.049
	0.431 < log alb < = 0.544	2.063	0.800		0.452	0.815	
	log alb > 0.544	1.451	0.563		0.334	0.601	
Serum AST at transplant 2	log AST < = 2.064	1.735	1.000	0.3294	0.381	1.000	0.006
	log AST > 2.064	5.446	3.138		1.214	3.183	
Serum ALT at transplant 2	log ALT < = 1.875	1.689	1.000	0.1741	0.372	1.000	0.003
	log ALT > 1.875	5.952	3.524		1.313	3.527	
Days on waiting list 2	Wait < = 88	1.893	1.000	0.0606	0.467	1.000	0.009
	Wait > 88	2.150	1.135		0.409	0.876	

*Death rate and graft failure rate (listed per 1,000 person months of follow-up)
1 = Significant variable in patient survival ($P < 0.05$)
2 = Significant variable in graft survival ($P < 0.05$)

instance, due to the chronic nature of EHBA very few patients in this group had evidence of either encephalopathy or received blood type mismatch transplants. The following variables were excluded from analysis: patient gender, ABO mismatch, more than one transplant, initial waiting list status, waiting list status at time of transplant, grades three-four encephalopathy at registration or LTx, life support at registration or LTx, or ventilator requirement at time of transplant. Of the 18 variables that were candidates for univariate analysis

TABLE 2. Cox Proportional Hazard Multivariate Analysis Demonstrating Significant Variables ($P < .05$ are in Bold) in the FHF and EHBA Groups

		Patient Survival		Graft Survival	
Variable	Variable category	Death Rate Ratio	p-value	Graft Failure Rate Ratio	p-value
Fulminant Hepatic Failure					
Patient age (years)	Age < = 2	2.552	<.0001	1.902	0.0002
	2 < Age < = 7	1.691	0.019	1.391	0.0532
	7 < Age < = 14	1.000		1.000	
	Age > 14	1.305	0.234	1.336	0.0803
Region	Region 1, 9, 10	1.404	0.191	1.081	0.6905
	Region 2, 3, 11	1.404	0.151	1.216	0.2534
	Region 4	1.931	0.019	1.272	0.2965
	Region 6, 7	1.678	0.046	1.445	0.0553
	Region 8	1.923	0.017	1.403	0.1157
	Region 5	1.000		1.000	
Blood type mismatch		1.611	0.011	1.545	0.0041
Life support at transplant		2.270	<.0001	1.692	<.0001
Life support at registration		1.489	0.015	1.579	0.0014
Donor age (years)	Donor age < = 7	1.000	—	1.000	—
	7 < Donor age < = 34	1.437	0.051	1.274	0.1032
	Donor age > 34	1.820	0.007	1.750	0.0014
Ventilator at registration		—	—	0.705	0.0290
Extrahepatic Biliary Atresia					
Medical condition at transpla	Not requiring ICU care	0.499	0.0001	0.698	0.0068
	Requiring ICU care	1.000	—	1.000	—
UNOS region	Region 1, 6, 11	4.317	<.0001	2.264	0.0002
	Region 3, 4	2.269	0.0045	1.731	0.0024
	Region 5	1.518	0.1788	1.066	0.7496
	Region 7, 8	1.662	0.0623	1.465	0.0209
	Region 9, 10	1.910	0.0372	1.497	0.0447
	Region 2	1.000	—	1.000	—
Type of liver graft	Split graft	1.761	0.0004	1.692	<.0001
	Whole graft	1.000	—	1.000	—
Ventilator at registration		—	—	4.481	<.0001

in the EHBA group, seven variables proved to be significant in patient survival and ten were significant in graft survival. These are listed and labeled appropriately in Table 1B.

Multivariate Analysis:

FHF group

Multivariate analysis of the FHF group revealed seven final variables that were simultaneously statistically significant for influencing patient survival (Table 2). These variables were the recipient's age, donor's age, the UNOS region of transplant, blood type mismatch, the presence of life support at registration and at time of transplant, and whether the patient underwent more than one LTx. With regards to graft survival in the FHF group, the UNOS region no longer was significant, while ventilator requirement at registration gained significance.

Extrahepatic biliary atresia analysis

In the multivariate analysis of the EHBA group for patient survival, the final list of predictors that were statistically significant included medical condition at time of transplant, region of transplant, and the type of graft received (Table 2). In addition to the same variables that influenced patient survival, ventilator requirement at registration also proved to be a significant factor in affecting graft survival in those patients transplanted for EHBA.

DISCUSSION

FHF in children is a poorly understood disease process, as evidenced by the lack of studies in the pediatric transplant literature.[8,9] Our Kaplan-Meier analysis of 5-year patient and graft survival reveals that both outcomes are significantly worse in those children who underwent transplantation for FHF as compared to EHBA. This finding has been suggested in previous studies with 1-year patient and graft survival rates.[10] Furthermore, multivariate analysis of the Studies of Pediatric Liver Transplantation database has shown that the diagnosis of FHF is a risk factor for both death and graft loss after LTx.[11] The strength of our analysis rests in the large sample size included in this study.

Due to the distinct nature of FHF and EHBA, we hypothesized that each group would have a unique set of variables that predict clinical outcomes. By performing univariate and multivariate analysis of the UNOS database from 1987 to 2002 we identified several distinct variables that influence the prognosis of pediatric LTx in FHF as compared to EHBA. The significance of this is that it demonstrates clear differences between these two groups of patients, indicating that the experience compiled from chronic liver disease patients cannot be simply extrapolated to the FHF group. Our data also confirms that the current method of allocation of liver grafts to pediatric transplant candidates by the PELD scoring system does not and should not pertain to children with FHF. The PELD scoring system was developed using the Studies of Pediatric Liver Transplantation database of pre-transplant children with chronic liver disease and evaluated the endpoints of death and transfer to the intensive care unit.[7] The PELD system attempts to predict the probability of mortality while on the waiting list as a means of allocating donor grafts in a fair and equitable manner. Fortunately, modifications made to the Organ Procurement TransplantationNetwork/UNOS policies in August of 2005 seek to address this issue. For pediatric patients Status 1 has been modified into statuses 1A and 1B. Status 1A will include revised definitions for FHF in that all patients in this category must have onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease, absence of pre-existing liver disease, location in an ICU, plus one of the following: a) ventilator dependence, b) dialysis or CVVH or CVVHD, or c) internal normalized ratio$>$ 2.0. The intent of these modifications is to ensure that the allocation priority assigned to Status 1A will be reserved for those children with FHF with the most immediate need for a liver transplant.

Our current study evaluates how various pre- and post-operative variables influence the risk of patient and graft survival following LTx for children with both chronic and acute liver disease. The significance of these individual risk factors in post-LTx patient and graft survival is addressed below.

Age of Recipient

While some studies on pediatric LTx have shown no difference in patient or graft survival by age,[12,13] others have demonstrated that recipient age significantly influences clinical outcome.[3,14,15] Once the distinction was made between FHF and EHBA patients, our analysis demonstrates that recipients less than seven years of age who underwent LTx for FHF had worse patient and graft survival rates when compared to older children (Table 2). This trend has been appreciated in a single-center pediatric study which described that recipient age of less than four years independently correlated with patient survival in children transplanted for FHF.[8] While small sample size was a limiting factor in the aforementioned study, the use of the UNOS database lends more credibility to this observation. Possible explanations of this trend may involve the age-specific differences in the underlying causes of FHF as well as the more difficult perioperative issues associated with younger patients. Further analysis of this important trend is required. Interestingly, the same trend was not appreciated in the group transplanted for EHBA. Possible reasons for this may include the fact that there is certainly more subjectivity as to when to refer and list children with FHF (as opposed to EHBA) for LTx. It is possible that younger children with FHF may not tolerate the delay in waiting for organs and LTx as well as children with chronic liver disease. The overall pre-LTx health status of children with FHF may be more tenuous than those with EHBA due to the fact that FHF may cause dysfunction of multiple organ systems resulting in increased ICP, cardiovascular instability, acute renal failure, coagulopathy and increased risk of infection .[16]

In patients with EHBA, age at transplantation, when stratified by <1 or >1 year old, has recently been shown in the SPLIT database to be a significant factor in predicting post-LT mortality. [17] This illustrates that the variability in many studies with regards to the importance of age may have a lot to do with the age cutoffs used for stratification and analysis.

Age of the Donor

While younger donor age previously has been reported to correlate with improved clinical outcomes in pediatric patients undergoing LTx, the majority of these studies focus on patients with chronic liver disease.[12,18] Our univariate analysis concurred with these results in patients with EHBA, in whom the death rate risk ratio was 2.0 for donors older than 6 years of age (Table 1B). However, our evaluation of the EHBA group by multivariate analysis did not reveal the donor age to significantly influence patient or graft survival.

In our evaluation of pediatric patients specifically transplanted for FHF, the donor age proved to be a significant variable that influenced patient and graft survival. Donor age greater than 34 correlated with a worse outcome for both patient and graft survival, donor age from 7 to 34 years of age approached significance for patient survival, while donors less than 7 years old had the best outcome in the FHF group (Table 2). Fortunately, the new UNOS criteria helps to ensure that pediatric donors will go to pediatric recipients.

Type of Graft

One of the many challenges in pediatric LTX includes the common use of reduced organ grafts. The current shortage of organ donors has led to the use of segmental grafts in order to provide timely liver transplants to children. Reports of increased graft loss with segmental grafts [13,19-21] have been confirmed by some transplant programs, while others report more encouraging results.[22,23] Most of these studies do not distinguish between the indications for LTx. In our multivariate analysis of patients transplanted for FHF, the type of graft received did not significantly

alter either patient or graft survival. However, receiving a reduced graft for the indication of EHBA negatively influenced both graft ($P < 0.0001$) and patient survival ($P = 0.05$) (Table 2). The finding of segmental grafts as a risk factor for patient survival in EHBA also supports a study by Goss et al. which evaluated 190 patients undergoing LTx for EHBA,[24] and a later multi-center analysis performed by the same group.[25] A possible explanation for this trend is that children with EHBA may tend to receive reduced-size grafts in emergent settings when their pre-LTx health is compromised. Additionally, children with EHBA on average undergo LTx at an earlier age than patients with FHF, which may predispose them to the technical challenges associated with small graft size, and prolonged stay in the intensive care unit. This trend warrants further study which may benefit from stratification of FHF by etiology and age.

ABO Mismatch

In a recent multivariate analysis of 500 pediatric LTxs, most of whom had chronic liver disease, ABO mismatch independently correlated with worse patient and graft survival.[12] Due to the infrequent need to transplant ABO mismatched organs in patients with chronic liver conditions such as EHBA, ABO mismatch was not analyzed in the EHBA group. However, mismatch was found to be a negative factor in the FHF group, impacting both patient ($P = 0.006$) and graft survival ($P = 0.004$). ABO mismatch has been reported in additional studies as predictive of worse graft survival in LTx for FHF.[26]

Children who receive ABO transplants are often quite sick at the time of LTx, and the physicians taking care of them are forced, so to speak, into accepting ABO mismatched organs for fear that the child may die on the waiting list while awaiting a properly matched organ. In this sense ABO mismatch may be somewhat of a confounding variable in that it interacts with variables such as life support, medical condition and ventilator status. Following this logic, in our multivariate analysis of the FHF group, ABO mismatch was still significant although to a lesser extent than it was in univariate analysis.

Medical Condition/Life Support/Ventilator Dependency

In multivariate analysis of patients transplanted for FHF, life support at registration and at transplant significantly influenced patient and graft survival (Table 2). In the EHBA group, the medical condition of the patient at time of transplant was a factor that significantly influenced patient and graft survival. Ventilator dependency at registration was found to negatively influence only graft survival in both EHBA and FHF groups. This is in contrast to the findings described in two studies where ventilator dependency pre-transplant correlated with actual survival of pediatric patients transplanted for FHF.[8,9]

UNOS Region

Regional differences influencing patient and/or graft survival in both groups were noted in our analysis. There is likely variability in referral patterns to transplant centers, as well as in the timing of registration and transplantation that may contribute to the disparity recorded in this study. The importance of referral patterns in influencing clinical outcome was previously reported in patients with FHF where it was noted that delays in transferring patients to a transplant center significantly affected the likelihood of survival.[27] Other studies have observed that donor selection criteria changed within transplant centers with additional experience.[28]

In terms of average waiting list time for pediatric patients, it has been shown that regional variations clearly exist.[29] The same analysis has revealed statistically significant differences by UNOS regions in the mean PELD scores and the percentage of children in the ICU at the time of transplant, perhaps suggesting regional variation in acuity of illness. Other studies have also demonstrated significant variation across the Organ Procurement Transplanation Network regions between PELD scores at the time of listing (range: 2-10) and transplant (range: 7-24).[30] Along these same lines it has been demonstrated that there is considerable variability in the relative availability of pediatric livers by region, and in the rate of pediatric liver transplantation relative to the census for a given region.[31] In terms of regional mortality rates on the pediatric waiting list there is little data available in the literature, and again while it is certainly an important area of study, it is one which is outside of the scope of this study. This regional variability warrants further study.

Repeat Transplants

Although we excluded actual repeat transplant episodes from our study, those patients who required more than one transplant were evaluated separately. By definition, repeat transplants indicated graft failure. While this variable could not be analyzed in the EHBA group, those patients who underwent LTx for FHF and required more than one transplant proved in univariate analysis to have a worse prognosis for patient survival (Table 1A). This is likely reflective of multi-system organ impairment prior to re-LTx.

Negative Findings

Serum creatinine and albumin at time of transplant, as well as prothrombin time and bilirubin levels from registration and transplant were not found to be significant in affecting patient or graft survival in those patients with FHF or EHBA in our study [32]. In terms of prothrombin time not being a significant predictor, this is likely in part due to the fact that that prolonged INR is often actively corrected in pediatric patients awaiting LTx in order to avoid complications associated with bleeding. This may make prothrombin time a less reliable indicator of a child's true synthetic liver function.

Another variable which was not a significant predictor in multivariate analysis of patient or graft survival for either group (EHBA or FHF), was time on the waiting list. This is likely because other variables more accurately describe and predict the gravity of a patient's health status at time of transplant. These include variables such as whether or not a patient requires ICU care or life support at the time of transplant, serum creatinine at time of transplant, and whether a patient received an ABO incompatible liver. The concept that patients' health status at the time of transplant plays an important role in survival is certainly not disputed by our analysis. We have simply shown that there are variables which more accurately describe patient acuity at the time of transplant and probability of surviving liver transplantation than the length of time on the waiting list. It is important to note that our analysis only examined survival for patients who make it to transplant. It does not measure the risk of dying on the waitlist as a result of longer wait times.

Study Strengths and Limitations

In comparison to prior small single center studies, the use of the UNOS database has granted us a large sample size in order to understand important cofactors in pediatric liver transplant outcome. More specifically our study includes the largest number of pediatric subjects who have undergone LTx for FHF. At the same time, a certain limitation of the UNOS transplant dataset is that the information contained within it was acquired from transplant centers with the objective of assuring proper allocation of organs. The use of multiple centers and covariates means that there is no assurance of data accuracy or completeness. An additional limitation is that the UNOS database does not include those patients who were not listed either because of precipitous recovery or clinical deterioration, including those patients never transferred to a transplant program. Furthermore, the UNOS database does not collect certain covariates, such as evidence of bone marrow dysfunction pre-LTx, which may be important predictors of outcome in children with FHF. Aplastic anemia is a relatively common and potentially significant problem in a subset of patients with fulminant hepatic failure. While our group and others have published single center experiences with aplastic anemia and FHF,[33,34] it would have been helpful to study such a problem using the extensive UNOS database. Unfortunately, aplastic anemia is not a variable which is captured in the UNOS database, therefore, it is not included this analysis.

Another weakness of the database is that the clinical laboratory values are limited to single points in time at registration and transplant, rather than a continuous trend; hence, peak laboratory values could not be evaluated as in other studies.[35,36] Nonetheless, the dataset contains valuable information that can be used to assess the transplant process.

Conclusion

In summary, there are several pre-transplant variables that influence pediatric patient and graft survival in FHF and EHBA. Given the current short supply of available organs, it is not only crucial that clinicians should be able to identify those patients in greatest need of a transplant, but also those who are most likely to survive surgery. This study provides such a list of important variables for children with both acute and chronic forms of liver disease requiring transplantation.

ACKNOWLEDGEMENT

The authors would like to acknowledge Jeff Gornbein of the Department of Biostatistics at the David Geffen School of Medicine at UCLA (Los Angeles, CA).

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