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SPECIAL ARTICLES

Risk factors and predictive indexes of early graft failure in liver transplantation

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A retrospective analysis of 462 consecutive liver transplantations has been carried out. These were divided into two groups, according to whether they failed within 90 days (Group I) or survived longer than 90 days (Group II). Twenty-five donor and recipient variables were analyzed. In the univariate analysis, the only donor variable that was significantly different between the two groups was age (45.3 ± 16.9 years in Group I vs 37.9 ± 15.4 years in Group II, p < 0.001). There were five recipient variables significantly associated with early graft failure: history of previous liver transplantations (p < 0.0001), United Network for Organ Sharing 4 status (p = 0.003), primary diagnosis (p = 0.001), preoperative serum creatinine (1.97±1.5 mg/dL in Group I vs 1.46 ± 1.2 mg/dL in Group II, p = 0.005), and preoperative total serum bilirubin (13.5±14.4 mg/dL in Group I vs 8.4±11.4 mg/dL in Group II, p = 0.003). In the multivariate analysis, only three variables were independently associated with outcome: donor age greater than 45 years, abnormal (> 1.5 mg/dL) recipient preoperative creatinine, and a history of previous liver transplantation.

Index terms: **Assessment of outcome model; Early graft failure; Liver transplantation; Predictors of transplantation failure.**

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Over the past 5 years, the yearly pool of cadaveric organ donors in the USA has remained stable at 4,500-5,000 (1). In 1989 there were 2,201 liver transplants (OLTx) performed in this country, increasing to 3,650 in 1994. However, this still falls far behind the estimated need (2). To meet the increasing demand for organs we need to pursue three parallel strategies: expanding the donor pool, by better defining donor predictors of failure (3-6); investigate alternative treatment modalities (bioartificial devices, xenotransplantation) (7-9); determine what preoperative factors, independently or in combination, predict the outcome of OLTx, allowing for a better management of this scarce resource.

The purpose of this study was to identify, from information that is usually available at the time of surgery, what risk factors are associated with early graft outcome after OLTx.

Patients and methods

Patient Population From January 1, 1992 to June 30, 1993, 438 consecutive adult patients received 481 liver transplants at the University of Pittsburgh Medical Center and the Veterans Administration Medical Center, Pittsburgh, PA. In 17 cases, the livers were part of multivisceral transplants that included intestine, and in other 2 cases were non-human livers (8, 9). These cases were not entered for analysis, leaving 419 recipients of 462 allografts. The information was obtained from the clinical database maintained by the Pittsburgh Transplantation Institute, and a review of the donor charts that are kept on file at the Center for Organ Recovery and Education (Western Pennsylvania Organ Procurement Organization) Pittsburgh, PA.

All grafts were flushed with the University of Wisconsin (UW) solution. ABO compatibility, size match, and medical urgency (UNOS status, see be-

riod with a documented infection, the decision to assign the death to sepsis or ischaemic injury was made based on whether there was poor function from the very beginning (i.e., a death from sepsis in a graft that never functioned well was coded as ischaemic injury). An exception to this rule is the patient who goes into the OLTx with an unrecognized infection (e.g., positive blood cultures which are not reported back until after the surgery), in which case the death was assigned to sepsis regardless of the degree of initial dysfunction. Cases in which the early failure was related to MODS (12) were also grouped with sepsis;

6. Other: self-explanatory.

Table II. Causes of early graft failures (Group I, n=84).

	Count	Percentage
Rejection*	2	2.4
Technical	9	10.8
Ischaemic injury**	36	42.9
Cardiovascular	8	9.5
Sepsis-MODS***	23	27.4
Other	6	7.2

*Includes acute and chronic rejection. **Includes primary non-function and delayed failure due to harvesting injury. ***MODS = Multiple Organ Dysfunction Syndrome. Group I = early graft failures (within 90 days).

Statistical Analysis

Univariate Continuous variables are presented as the mean ± standard deviation (SD), and categorical variables as rates. A two-tailed t-test was used to test for differences between means, and Pearson's chi-square to test for differences between rates.

Multivariate Variables found, by univariate analysis, to be associated with outcome, or whose association was of borderline significance, were then used in a stepwise logistic regression analysis to identify the variables that are independent predictors of outcome. In the case of categorical variables, preliminary univariate logistic regression models were fit to determine if sub-categories should be grouped together. Similarly, in the case of continuous variables preliminary logistic regression analysis was used to determine if they were more appropriately represented as categorical variables. Models were fit using both forward inclusion and backward elimination, with a likelihood ratio test. A significance level of 0.1 was used in the stepwise procedure.

All procedures were performed using SPSS (Statistical Package for the Social Sciences, SPSS, Inc. Chicago, Illinois).

Results

Demographics Follow-up ranged from 1.12 to 2.6 years. Of the 462 livers, 452 were transplanted alone and the rest were combinations with a kidney (n=4), bone marrow (n=4), heart (n=1), and pancreatic islets (n=1). The only ABO mismatch, A to O, was successful. Of the 144 graft losses (31.2%) during the study period, 84 (18.2%) were within the first 90 days (early graft failures).

Effect of putative risk factors As shown in Table III, in the univariate analysis the only donor variable that was significantly different between the two groups was age ($p < 0.001$). Donor sex reached borderline significance (p=0.068). Since the mean harvest serum sodium was lower in the early failure group (147±11 mEq/L in Group I vs 150±11 mEq/L in Group II, $p = 0.09$) contrary to reports by other groups (13), the analysis was repeated after grouping it into physiologically meaningful ranges (Table III). Subsequent multivariate analysis used both representations.

There were five recipient variables (Table IV)

Table III. *Donor variables according to outcome.*

	Group I (n = 84)	Group II (n = 378)	Significance
Age (yrs)	45.3±16.9	37.9±15.4	p < 0.001
Female sex (%)	45.2	34.7	p = 0.068
ICU LOS (days)	3.8±4.1	3.5±5.1	p = 0.58
Pressors (%)	42.5	39.7	p = 0.64
Pitressin (%)	38.8	29.3	p = 0.1
CPR (%)	16.3	17.3	p = 0.82
Terminal AST (IU/L)	64±54	76±86	p = 0.2
Terminal ALT (IU/L)	47±40	51±66	p = 0.63
Ischaemia time (hr)	13.3±2.9	13.3±3.7	p = 0.9
Harvest serum sodium (%)			
< 136	15.7	7.4	
136 to 145	27.1	27.9	
146 to 160	44.3	47.9	
> 160	12.9	16.8	p = 0.15
Cause of death (%):			
Anoxia	6.0	8.0	
Closed head injury	8.3	9.0	
Stroke	52.4	36.4	
Trauma	22.6	33.0	
Other	10.7	13.6	p = 0.1

Group I = early graft failures (within 90 days). Group II = successful grafts or grafts that failed later (>90 days post-transplant)

Table IV. *Recipient variables according to outcome.*

	Group I (n = 84)	Group II (n = 378)	Significance
Age (yrs)	50.9±12.3	51.0±12.0	p = 0.945
Sex (m/f)	58/26	241/137	p = 0.36
Prior OLTx (%)	33.3	12.2	p = 0.0001
UNOS 4 status (%)	57.1	39.2	p = 0.003
Waiting time (days)	116±242	151±270	p = 0.283
Positive crossmatch (%)	9.6	10.3	p = 0.85
Preoperative creatinine (mg/dL)	1.97±1.5	1.46±1.2	p = 0.005
Preoperative bilirubin (mg/dL)	13.5±14.4	8.4±11.4	p = 0.003
Primary diagnosis (%):			
Alcoholic	14.3	17.2	
Cholestatic	17.9	19.0	
Cryptogenic	14.3	9.8	
FHF	1.2	1.1	
PNF-ischaemia	14.3	2.9	
HCC-cholangio	3.6	7.4	
Metabolic	2.4	1.9	
Hepatitic	22.6	30.7	
Rejection	1.2	0.3	
Technical	4.8	1.6	
Other	3.4	8.1	p = 0.001

Group I = early graft failures (within 90 days); Group II = successful grafts or grafts that failed later (>90 days post-transplant)

significantly associated with early graft failure: history of previous OLTx ($p < 0.0001$), UNOS 4 status ($p = 0.003$), primary diagnosis ($p = 0.001$), preoperative creatinine ($p = 0.005$), and preoperative bilirubin ($p = 0.003$).

The variables that reached significance or borderline significance were then entered into a stepwise logistic regression analysis to identify the independent predictors of early graft failure. Only three variables were independently associated with this outcome: donor age greater than 45 (odds ratio 2.0, 95% CI 1.3 to 3.3), abnormal (> 1.5 mg/dL) recipient preoperative creatinine (odds ratio 1.9, 95% CI 1.1 to 3.2), and a history of previous OLTx (odds ratio 2.7, 95% CI 1.5 to 5.0). However, when serum creatinine was withheld from the analysis, UNOS 4 status then became an independent predictor.

Eighty-four grafts failed early, ischaemic injury and sepsis-MODS being the leading causes (Table II).

Discussion

Since 1982, OLTx has become definitely established in the treatment of end-stage liver diseases (14). In that year, it was estimated that the annual need for OLTx was 15 per million population (14), but this is now higher, as the advances of the past decade allow us to treat patients that not long ago, would have been considered not transplantable (15). But, while in the past, the appropriateness of the decision to proceed with transplantation was judged largely on the basis of technical and medical factors related to the recipient, nowadays it is the supply of organs that increasingly shapes these decisions. The limited supply has been used, at some institutions, to justify restricting the availability of the procedure, a concept with which we disagree (16). We have previously demonstrated that, in specific disease categories, the most important gain in survival is in patients that belong in the highest pretransplant risk groups (16, 17). Therefore, sicker patients should be treated first, but in order to make the best use of our limited societal donor resources a number of authors, in the last few years, have dedicated their attention to identify pre-transplant parameters (immunological, biochemical, and clinical) which might be useful in predicting the outcome of the OLTx. Shaw et al. (18) have reported the influence, on the six-month survival rate after OLTx, of 11 clinical and laboratory variables in 160 adult liver recipients. In their study, survival at six months was found to correlate inversely with operative blood loss, coma, malnutrition, serum bilirubin, prothrombin time; and directly with the date of transplant. It did not correlate to a significant degree with the recipients' age, sex, race, presence of ascites, previous surgery, or diagnosis. The effects of pre-operative bilirubin and the degree of malnutrition (scored on the basis of the serum albumin level) have been disputed by Baliga et al. (19) who analyzed 31 pre-operative variables in a series of 229 adult OLTx. In their study, admission to the intensive care unit immediately before OLTx, a serum creatinine level >1.7 mg/dl, and Child-Pugh class C were associated with a significant higher incidence of hospital mortality rate. Cuervas-Mons et al. (20) correlated 27 clinical and laboratory data with the subsequent clinical course of 93 adult OLTx recipients and found that 7 variables (ascites, encephalopathy, elevated white blood cells and polymorphonuclear cell count, decreased helper to suppressor T cell ratio, and elevated serum creatinine and bilirubin levels) were associated with a significantly increased risk of mortality. In their series, a serum creatinine ≥1.72 mg/dl predicted survival or death in 79% of cases.

A transplant is the result of the combination of two complex biological systems (the donor and the recipient) and their physiological and pathological status.

Therefore, it is better to try to identify pre-operative risk factors using both donor and recipient variables, instead of limiting the analysis to the recipient data. In our study, we analyzed only those parameters that are obtained as part of a routine pre-transplant recipient and donor work-up, always available at the time of the donor allocation. Our idea was to select simple parameters in a way which could be uniformly reproduced by other surgeons in the field. In fact, variables like encephalopathy, nutritional status, and degree of ascites might be biased by subjective judgement, while others, like helper to suppressor T cell ratio or the number of documented episodes of spontaneous bacterial peritonitis, might not be routinely available.

There is a wealth of anecdotal experience regarding the deleterious effects of donor hypernatraemia, and they have recently received some support from clinical studies (13). In the current study, however, we failed to find corroborative evidence, and these results are consistent with those we obtained in a much larger series (21). One possible explanation for the perception of hypernatraemia as a risk factor is the fact that over 60% of our donors are hypernatraemic, as a result of the management of their neurologic pathology. Therefore, assuming that the probability of failure is the same in hyper- and normonatraemic donors, we should expect the majority of failed grafts to come from hypernatremic donors (although the proportions would be the same). We should also point out that our endpoint, graft failure, is different from that of Gonzalez et al. (13), who studied the correlation of donor serum sodium with a scoring system they developed. How well that scoring system correlates with the probability of the graft failing is unclear. We still cannot rule out the possibility that extreme values of donor serum sodium, either too low or too high, increase the risk of the graft, since the number of observations in the extreme ranges is relatively small. Only more experience with these donors will provide the answer.

The results of our multivariate analysis indicate that livers procured from donors older that 45 are at a significantly higher risk of early failure (odds ratio 2.0, 95% CI 1.3 to 3.3). The adverse effect of increasing donor age had been surmised from the start of clinical liver transplantation, when a ceiling of 45 years was recommended for donor selection (22). Over the ensuing years a number of reports appeared suggesting that outcome was not effected by donor age (23, 24). However, we recently demonstrated that livers from donors older than 60 years have only a 43% 2-year survival, vs 71% for the younger donors (25). A detailed analysis revealed that the risk of failure, as a function of donor age, remains constant until age 45 years, and then increases sharply (4). The adverse influence of female donor sex was clearly demonstrated on the late outcome (4).

In the current study, the livers from female donors did not have a worse prognosis, in terms of early outcome (i.e., within 90 days). However, in a larger study we just completed, where we focused on the effect of the cytotoxic crossmatch, donor sex was found to be independently associated with early graft failure (21). The reasons for this discrepancy are probably twofold: sampling effect (462 grafts in the current study vs 1,520 in the crossmatch study), and slightly different endpoints (failure at 90 days, in the current study, vs failure at 180 days, in the crossmatch study). The different choice of endpoints was dictated by the problem under investigation (21).

The two other variables that were found to be independently associated with early graft failure were abnormal recipient pre-operative creatinine (greater than 1.5 mg/dL, odds ratio 1.9, 95% CI 1.1 to 3.2) and a history of previous OLTx (odds ratio 2.7, 95% CI 1.5 to 5.0). However, when serum creatinine was withheld from the logistic regression analysis, UNOS 4 status became an independent predictor. These results, and those of recently completed studies (4, 21, 25, 26), are helping us to lay the foundation of a better understanding of the complex interactions that determine the outcome of liver transplantation. Incidentally, it is instructive to see how a simple biological measurement, such as serum creatinine, has a greater explanatory power than an administrative medical urgency classification system, such as UNOS status. As we continue to work towards refining our organ allocation systems, we should strive to let the biology of the process lead the way.

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References

1. Marino IR, Doyle HR, Fung JJ Liver. In: Higgins RSD, Sanchez JA, Lorber MI, Baldwin JC (Eds), The Multiorgan Donor. Blackwell Science, Inc., Publisher, Cambridge, MS. In press.
2. Starzl TE, Demetris AJ, Van Thiel DH. Medical progress: Liver transplantation. N Engl J Med 1989; 321(15): 1014-22.

3. Makowka L, Gordon RD, Todo S, et al. Analysis of donor criteria for the prediction of outcome in clinical liver transplantation. Transplant Proc 1987; 19(1): 2378-82.
4. Marino IR, Doyle HR, Aldrighetti L, et al. Effect of donor age and sex on the outcome of liver transplantation. Hepatology 1995; 22(6): 1754-62.
5. Pruim J, Klompmaker IJ, Haagsma EB, Bijleveld CMA, Sloof MJH. Selection criteria for liver donation: a review. Transpl Int 1993; 6(4): 226-35.
6. Strasberg SM, Howard TK, Molmenti EP, Hertl M. Selecting the donor liver: risk factors for poor function after orthotopic liver transplantation. Hepatology 1994; 20(4): 829-38.
7. Rozga J, Podesta L, LePage E, et al. Control of cerebral oedema by total hepatectomy and extracorporeal liver support in fulminant hepatic failure. Lancet 1993; 342(8876): 898-9.
8. Starzl TE, Fung JJ, Tzakis A, Todo S, Demetris AJ, Marino IR, et al. Baboon to human liver transplantation. Lancet 1993; 341(8837): 65-71.
9. Starzl TE, Valdivia L, Murase N, et al. The biologic basis of and strategies for clinical xenotransplantation. Immunol Rev 1994; 141: 213-44.
10. Takaya S, Iwaki Y, Starzl TE. Liver transplantation in positive cytotoxic crossmatch cases using FK506, high-dose steroids, and prostaglandin E1. Transplantation 1992; 54(5): 927-9.
11. Starzl TE, Demetris AJ. Liver Transplantation. A 31-Year Perspective. Year Book Medical Publ, Inc., Chicago, 1990.
12. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101(6): 1644-55.
13. Gonzalez FX, Rimola A, Grande L, et al. Predictive factors of early postoperative graft function in human liver transplantation. Hepatology 1994; 20(3): 565-73.
14. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982; 2(5): 614-36.
15. Doyle HR, Marino IR, Miro A, et al. Adult respiratory distress syndrome secondary to end-stage liver disease. Successful outcome following liver transplantation. Transplantation 1993; 55(2): 292-6.
16. Eghtesad B, Bronsther O, Irish W, et al. Disease gravity and urgency of need as guidelines for liver allocation. Hepatology 1994; 20(1 Pt. 2): 56S-62S.
17. Abu-Elmagd KM, Malinchoc M, Dickson ER, et al. Efficacy of hepatic transplantation in patients with primary sclerosing cholangitis. Surg Gynecol Obstet 1993; 177(4): 335-44.
18. Shaw BW, Wood RP, Gordon RD, Iwatsuki S, Gillquist WP, Starzl TE. Influence of selected patient variables and operative blood loss on six-month survival following liver transplantation. Semin Liver Dis 1985; 5(4): 385-93.
19. Baliga P, Merion RM, Turcotte JG, et al. Preoperative risk factor assessment in liver transplantation. Surgery 1992; 112(4):704-11.
20. Cuervas-Mons V, Millan I, Gavaler JS, Starzl TE, Van Thiel DH. Prognostic value of preoperatively obtained clinical and laboratory data in predicting survival following orthotopic liver transplantation. Hepatology 1986; 6(5): 922-7.
21. Doyle HR, Marino IR, Morelli F, et al. Assessing risk in liver transplantation - With special reference to the significance of a positive cytotoxic crossmatch. Ann Surg. In press.
22. Starzl TE The Liver Donor. And, Appendix of Case Material and Bibliography. In: Starzl TE (Ed), (with the assistance C.W. Putnam). Experience in Hepatic Transplantation. WB Saunders Co., Philadelphia, 1969: 16-21 & 528-45.
23. Teperman L, Podesta L, Mieles L, Starzl TE. The successful use of older donors for liver transplantation. JAMA 1989; 262(20): 2837.
24. Wall WJ, Mimeault R, Grant DR, Bloch M. The use of older donor livers for hepatic transplantation. Transplantation 1990; 49(2): 377-81.
25. Marino IR, Doyle HR, Doria C, et al. Outcome of liver transplantation using donors 60 to 79 years of age. Transplant Proc 1995; 27(1): 1184-5.
26. Doyle HR, Marino IR, Jabbour N, et al. Early death or retransplantation in adults after orthotopic liver transplantation. Can outcome be predicted? Transplantation 1994; 57(7): 1028-36.