Risk Stratification of Adult Patients Undergoing Orthotopic Liver Transplantation for Fulminant Hepatic Failure

Neal R. Barshes,[1] Timothy C. Lee,[1] Rajesh Balkrishnan,[2] Saul J. Karpen,[1,3] Beth A. Carter,[3] and John A. Goss[1,4]

Background. Orthotopic liver transplantation (OLT) is an effective treatment for fulminant hepatic failure (FHF), but postOLT mortality is higher for patients with FHF than for patients with other indications for OLT. In the current study, a large cohort of patients who underwent OLT for FHF was evaluated to develop and validate a system useful for estimating postOLT patient survival.

Methods. The 1,457 patients who underwent OLT for FHF in the United States between 1988 and 2003 were enrolled through the UNOS database. This group was divided into a modeling group (n=972) and a crossvalidation group (n=486). With a multivariate regression analysis, the modeling group was used to identify clinical parameters that had a significant association with postOLT survival. This regression analysis was used to create a scoring system that was subsequently assessed in the crossvalidation group.

Results. Four risk factors were identified with the multivariate analysis: 1) body mass index $\geq$30 kg/m^2; 2) serum creatinine $>$2.0 mg/dL; 3) recipient age $>$50 years old; and 4) history of life support. By assigning points based on the number of risk factors present, the scoring system was able to differentiate between low-risk patients (5-year survival, 81%) and high-risk patients (5-year survival, 42%). The relative risk of postOLT mortality increased by approximately 150% for each additional point.

Conclusion. The scoring system risk-stratified the crossvalidation group and accurately predicted postOLT survival. A scoring system utilizing clinical and demographic information readily available prior to OLT may help predict the probability of survival after OLT for FHF.

Keywords: Modeling, Survival, Prognostic.

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Fulminant hepatic failure (FHF), defined as the onset of encephalopathy within 8 weeks of hepatic symptoms in the absence of preexisting liver disease (*1*), occurs with an incidence of approximately 2,000 cases/year in the United States. Orthotopic liver transplantation (OLT) is the only treatment option for cases of FHF in which the native liver does not recover spontaneously. Patient survival after OLT for FHF ranges between 40% and 80% at 1-year postOLT (*2*) and is generally poorer than the patient survival after OLT for most other indications (*3*). Considering the fact that an inadequate supply of donor livers often limits the application of OLT, it has been argued that the allocation of liver grafts to patients should take into account the likelihood of postOLT survival (*4*).

The probability of patient survival following OLT for FHF has been estimated using regression equations (*4–6*). Risk stratification schemas specific to FHF may help clinicians estimate survival of patients with FHF who are candidates for OLT. Previous attempts at risk stratification of this population have focused on demographic features and laboratory test results to identify patients that would benefit from OLT. Variables such as serum creatinine level and age $<$1 year have been identified as having prognostic value, but all previous multivariate analyses of FHF postOLT survival have been derived from single center patient populations and have not been cross-validated. Hence it is not clear if these variables would be useful to predict patient survival after OLT for FHF in a more heterogeneous population. Furthermore, regression equations, although able to provide accurate estimates of survival for groups of patients, are often inconvenient and unwieldy for the clinician at the bedside. A simplified approach to estimating patient survival would provide more utility.

In the current study, we applied a multivariate regression analysis to a large population of patients who underwent OLT for FHF with the objective of identifying risk factors for postOLT mortality. The relative influence of these risk factors was then used to create a scoring system to assist clinicians in the risk stratification of patients with FHF undergoing OLT. A regression analysis was used to create a simple, novel scoring system that was subsequently cross-validated. Using this cross-validated risk stratification scoring system, clinicians can accurately estimate the probability of patient survival for patients undergoing OLT for FHF.

METHODS

Patient Population

Patient studied in this report were enrolled through the United Network for Organ Sharing (UNOS) Organ Procure-

[1] Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX.
[2] Division of Management, Policy, and Community Health, University of Texas Health Sciences Center School of Public Health, Houston, TX.
[3] Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Baylor College of Medicine, Houston, TX.
[4] Address correspondence to: John A. Goss, M.D., Liver Transplantation, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, 6550 Fannin, Suite 1628, Houston, TX 77030.
E-mail: jgoss@bcm.tmc.edu
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ment and Transplantation Network database. This registry includes the survival data of patients who have undergone OLT in the United States between January 1988 and January 2004. Inclusion criteria included a primary diagnosis of fulminant hepatic failure, age >18 years old, and UNOS status 1. Patients were excluded if the time interval between initial listing and transplantation was more than 30 days, or if a history of previous organ transplant was present. After enrolling patients using the inclusion and exclusion criteria, 1,457 patients remained.

This cohort of 1,457 patients was then randomly divided into two subsets, containing approximately 66% and 33% of the total cohort (972 and 486 patients, respectively) (*7*). The larger (66%) subset was used to formulate a postOLT survival model (referred to subsequently as the "modeling group"). The smaller (33%) subset was later used to cross-validate the final model generated ("cross-validation group").

Statistical Methods

Descriptive data were used to examine the baseline characteristics of the modeling and cross-validation groups. Categorical variables of the modeling and cross-validation groups were compared with the Pearson's chi-squared calculation, and continuous variables were compared with a Student's *t* test. Variables were selected for univariate analysis based on availability and completeness of data in the OPTN database as well as biological plausibility. Continuous variables were examined as such and also as categorical variables after stratification into quartiles. Certain variables were also stratified based on clinically-relevant limits or criteria, including body mass index (BMI) (*8*), creatinine (*9*), and age (*10*).

Covariates that were significant at the modest level of 20–25% in the univariate analysis were included in a multivariate regression analysis. This was performed using a Cox proportional hazard model with $P<0.05$ considered statistically-significant. The final model was chosen based on statistical significance and clinical relevance of the variables. All statistical analyses were performed with SPSS version 11.0 (SPSS Corporation, Chicago, IL).

RESULTS

Pretransplant Characteristics, Patient and Graft Survival, and Causes of Death following OLT for FHF

Patient demographics and peritransplant variables are listed in Table 1. The modeling and cross-validation groups were similar in all variables assessed; no statistically-significant differences were found between the two groups. Approximately 50% of all cases in each group were due to unknown or miscellaneous causes, one-quarter were drug-induced, and another quarter were viral in origin. In all, more than 97% of patients in each group received a cadaveric whole-organ liver graft; 1.2% and 2.9% of patients in the modeling and cross-validation groups, respectively, received cadaveric split-liver grafts ($P=0.16$) Only 13 patients (0.9%) in either cohort have received grafts from living donors; eight of these were right grafts, one was a left graft, one was a left lateral segment graft, and the type of the remaining three grafts were unspecified.

The overall patient survival for the modeling group was 77.1%, 67.2% and 60.0% at 1, 5, and 10 years postOLT, respectively (Fig. 1). Survival in the cross-validation group was similar: 78.3% at 1 year, 67.4% at 5 years, and 58.8% at 10 years postOLT. A log-rank test showed no differences between these survival rates ($P=0.74$). Graft survival was 69.2%, 57.1% and 48.3% in the modeling group and 71.7%, 58.7% and 48.8% in the cross-validation group at 1, 5, and 10

TABLE 1. Patient demographics and peritransplant variables of the three groups used in this study

Variable	Modeling group	Cross-validation group	*P* value
n	972	486	
Age (years)	33	38	0.97
Male (%)	33.5	32.7	0.75
Diagnosis			0.17
Drug-induced	20.8%	24.3%	
Viral hepatitis	28.1%	24.2%	
Other/unknown	51.1%	51.5%	
Body mass index (kg/m^2)	25.9	25.4	0.45
History of life support (%)	63.8	65.2	0.61
History of encephalopathy (%)	80.7	77.1	0.17
Total bilirubin (mg/dL)	22.0	21.6	0.67
Serum creatinine (mg/dL)	1.2	1.2	0.87
Donor weight (kg)	71.0	72.0	0.61
Donor age (years)	33	36	0.20
Days on waiting list	1.0	2.0	0.13
Warm ischemia time (minutes)	48	48	0.40
Cold ischemia time (minutes)	486	484	0.84
Graft type			0.16
Whole	98.3%	97.1%	
Split/reduced	1.7%	2.9%	

P values refer to comparisons of modeling group with the cross-validation group.

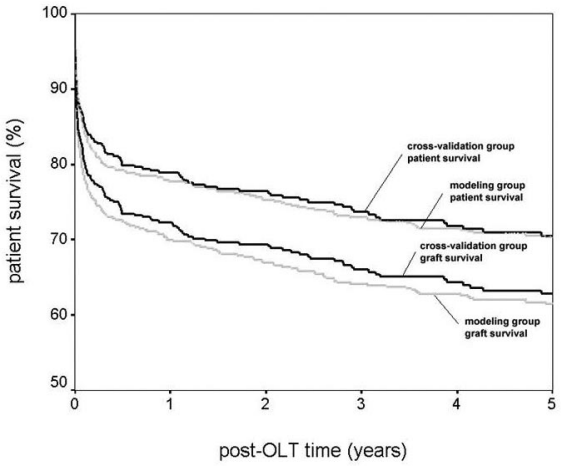

FIGURE 1. Kaplan-Meier curves demonstrating patient and graft survival following OLT for fulminant hepatic failure. The modeling group (n=972) is represented by the grey lines and the cross-validation group (n=486) is represented by the black lines.

years postOLT, respectively. The graft survival rates of the two groups did not differ significantly (P=0.88).

The causes of death following OLT were examined in the modeling group. In all, 266 deaths were recorded in that group. Infection was the most common cause of mortality following OLT for FHF, accounting for 67 deaths (23.6% of postOLT deaths). Of these, approximately 50% (34 deaths) were due to generalized sepsis. Fungal infections accounted for another 15 deaths (5.6% overall). Brain death was the second most common cause of mortality, resulting in 35 postOLT deaths (13%). These cases include deaths due to cerebral edema, cerebral herniation, hemorrhagic stroke as well as patients that never recovered neurological function after transplantation. Multiple organ-system failure was the third most frequent cause of mortality, resulting in 25 deaths (9.4%).

Six intraoperative deaths occurred (2.3% of postOLT deaths). Twelve patients (4.5%) died secondary to primary non-function. Only one death (0.4%) was attributed to vascular thrombosis of the graft, while biliary complications accounted for an additional three deaths (1.1%). Other causes of mortality following OLT for FHF included: cardiac complications (9.0%), respiratory failure (3.4%), malignancy (1.9%) and renal failure (1.1%). The cause of death of 39 patients (14.7%) was listed as "other" or unknown.

Univariate and Multivariate Analysis

A total of 14 variables were analyzed for possible relationship to postOLT survival at 1 and 5 years using Cox proportional hazards univariate analyses. Those that were found to have a statistically-significant correlation on patient survival included: recipient body mass index (BMI), serum creatinine, log serum creatinine, history of life support (including mechanical ventilation, vasopressors, intraaortic balloon pump, extracorporeal membrane oxygenation or prostaglandin E infusion), donor age, donor gender, recipient age >50 years old and recipient gender. Liver graft type, total serum bilirubin, log total serum bilirubin, donor body weight, donor graft cold ischemia time, donor graft warm ischemia time, time on transplant waiting list and etiology (viral vs. drug-induced vs. other/unknown) were found to have no statistically-significant association with survival.

A multivariate Cox proportional hazards analysis was performed to identify independent risk factors for patient mortality following OLT for FHF. The final model contained four such variables, each determined at the time of listing for transplantation: 1) BMI $\geq$30 kg/m^2 (i.e. obesity); 2) serum creatinine >2.0 mg/dL; 3) age >50 years old; and 4) history of life support. The hazard ratios, 95% confidence intervals, and P values for these variables are listed in Table 2.

Modeling Risk Stratification of Patients with FHF Undergoing OLT

The regression coefficients for the four variables identified by multivariate analysis were similar (Table 2), and it was apparent that risk stratification could be simplified by averaging the amount of risk associated with each risk factor and creating a point system. Patients were given one point for the presence of any of the four risk factors at the time of transplant registration, assigning each patient a total that ranged from 0 to 4 points (Table 3). This effectively stratified all patients in the modeling group into one of five groups based on risk as determined by the multivariate regression analysis. Approximately 14% of patients in the modeling group had 0 points, 37% had one point, 33% had two points, 14% had three points, and 2% had four points. To verify that the outcomes were indeed consistent with the predicted risk, patient survival was examined for each individual point total. As shown in Figure 2A, the analysis of patient survival for each of the five strata demonstrated that this risk stratification schema did indeed predict probability of postOLT mortality in patients undergoing OLT for FHF. In other words, the total number of points merited was directly correlated with an increased risk of postOLT mortality. A log-rank test revealed

TABLE 2. Multivariate regression analysis results of patient 5-year survival for the modeling group of patients undergoing orthotopic liver transplantation for fulminant hepatic failure (n=972)

Variable	Hazard ratio	95% confidence interval		*P* value
		Lower	Upper	
Body mass index $\geq$30 kg/m^2	1.52	1.12	2.06	0.008
Serum creatinine >2 mg/dL	1.43	1.05	1.95	0.022
Age >50 years old	1.39	1.003	1.928	0.048
History of life support	1.38	0.992	1.914	0.056

TABLE 3. Proposed criteria for risk stratification of patients undergoing orthotopic liver transplantation for fulminant hepatic failure

Criteria	Points
Body mass index ≥30 kg/m^2	1
Serum creatinine >2 mg/dL	1
Age >50 years old	1
History of life support	1
Total	0–4

Applicable for UNOS status I patients; points are tallied at the time of listing for transplantation.

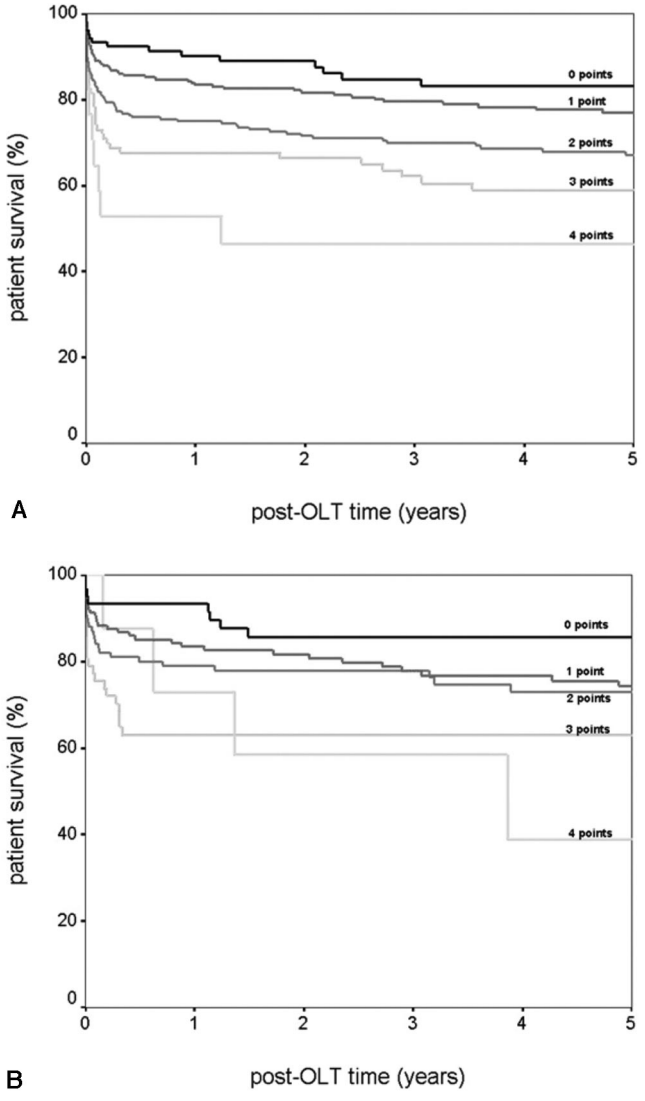

FIGURE 2. Kaplan-Meier postOLT survival estimate for the patients undergoing OLT for FHF in (A) the modeling group (n=972) and in (B) the cross-validation group (n=486).

that these survival rates for these strata differed significantly from one another ($P<0.0001$).

A Cox proportional hazards regression analysis further showed that the number of points present was significantly

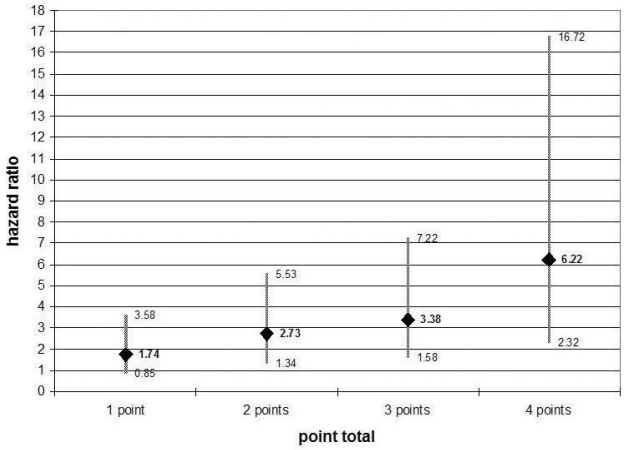

FIGURE 3. Hazard ratios and corresponding 95% confidence intervals for the modeling group (n=972).

correlated with postOLT mortality rates ($P<0.00001$). The average hazard ratio was 1.49, with a confidence interval of 1.26–1.77. The exact hazard ratios and corresponding 95% confidence intervals for each individual stratum are presented in Figure 3. This signifies that at any point in time, the relative risk of death increases by about 150% for each point merited by an individual patient. The 1-year postOLT survival rates for patients undergoing OLT for FHF worsened with an increasing number of points (Fig. 2A): 1-year patient survival was 89.7% for patients with zero points; 83.0% for patients with one point; 73.6% for patients with two points; 67.2% for patients with three points; and 51.5% for patients with four points. The differences between the strata at 5-year postOLT were even more pronounced: 81.3% for 0 points; 74.3% for 1 point; 63.2% for 2 points; 57.4% for 3 points; and 41.9% for 4 points.

Cross-validation

The other third of the cohort (n=472) was examined to cross-validate the risk stratification schema. These patients were stratified according to risk of postOLT mortality based on the point system. Approximately 15% of patients had no risk factors, 39% had one, 28% had two, 16% had three and 2.3% had all four risk factors present. The five year postOLT survival of the cross-validation group was compared to that of the modeling group for each individual stratum (point total) using a log rank test. All analyses showed no statistically-significant differences in 5-year survival when these two groups were compared. Finally, a Cox proportional hazard regression analysis showed a significant positive correlation between the number of points and risk of postOLT mortality ($P<0.0001$). In particular, the relative risk of postOLT mortality increased 162% with every additional point merited by the patient (95% confidence interval 129%–204%). As in the modeling group, survival of the cross-validation group patients during the first 5 years postOLT worsened with an increasing number of points (Fig. 2B). Specifically, 1-year patient survival rates were 93.1% for those with no points, 83.2% for those with one point, 78.6% for those with two points, 61.1% for those with three points, and 75.0% for those with four points. The 5-year postOLT survival rates for the

cross-validation group strata were very similar to that of the modeling group strata: 83.2% for zero points; 73.1% for one point; 68.5% for two points; 55.6% for three points; and 46.7% for four points.

An additional cross-validation was performed with adult patients that underwent OLT for all non-FHF indications between 1988 and 2004. The results of this analysis demonstrate the ability of the risk stratification schema to be applied to non-FHF patients (Fig. 4). One-year survival rates for all non-FHF patients were 89.2% for those with no points, 85.3% for those with one point, 79.5% for those with two points, 65.3% for those with three points, and 53.5% for those with four points. The 5-year postOLT survival rates for these non-FHF patients were 77.6% for those with no points, 71.0% for those with one point, 65.9% for those with two points, 53.9% for those with three points, and 41.3% for those with four points.

DISCUSSION

After proposing their own criteria for identifying potential candidates for OLT among patients with FHF, O'Grady et al. from King's College Hospital in London stated that the "ideal" patient selection criteria for OLT in the setting of FHF would be "derived from a large, mixed population; prospectively validated; simple and reproducible; applicable early in the course of illness; high positive and negative predictive values; on-going validation and refinement" (*11*). Such criteria have been difficult to generate for an indication such as FHF, as FHF occurs infrequently enough to prevent all but the largest transplant centers from accumulating a significant experience with the disease process.

The purpose of this study was to identify risk factors available to the clinician at the time of transplant registration and to quantify the relationship between these risk factors and patient survival after OLT for FHF. After screening 14 biologically-plausible clinical variables with univariate analyses, selected variables were entered into a multivariate analysis. The final multivariate model identified four risk factors, each determined at the time of listing for transplantation, that were associated with a decreased likelihood of patient survival after OLT: 1) history of life support; 2) recipient age >50 years old; 3) recipient BMI ≥30 kg/m^2; and 4) serum creatinine >2.0 mg/dL. The additional risk to postOLT patient survival posed by each of these risk factors was additive, so a scoring system was used to create a model to estimate patient survival after OLT for FHF. One point was given to a patient for each one of the four above mentioned risk factors present at the time of listing for transplantation. Thus a risk-stratification score ranging from 0 to 4 is generated, with an increasing number of points signifying increasing risk of postOLT mortality (Table 3).

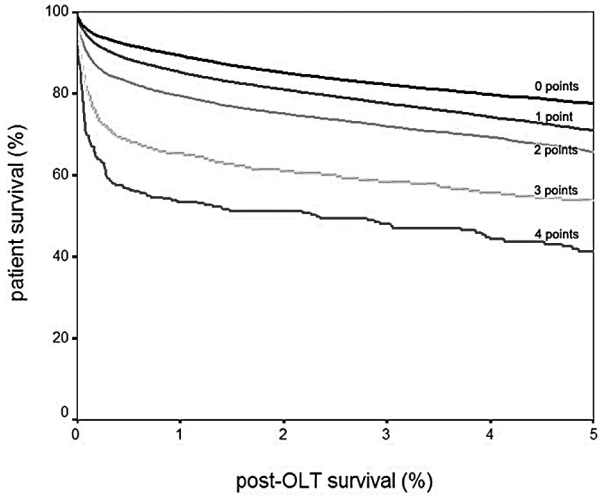

FIGURE 4. Kaplan-Meier postOLT survival estimate for patients undergoing OLT for all non-FHF indications (n=44,170).

This scoring system may be used for risk stratification of patients undergoing OLT for FHF. Using this risk stratification system, patients with the maximum score of four points (i.e. all four risk factors present, denoting high risk) had a 5-year postOLT survival rate of 43.5%. In contrast, patients with no points (i.e. no risk factors present, low risk) had a 5-year postOLT survival rate of 82.0%, roughly double that of the high risk patients. When this risk-stratification scoring system was applied to the cross-validation group, similar survival rates were seen: 46.7% 5-year survival for the highest risk patients (4 points) versus 83.2% for the lowest risk patients (no points). When used as a covariate in a Cox proportional hazard model, the proposed risk-stratification scoring system has a hazard ratio of 1.5. This means that for each additional risk factor present at the time of listing for transplantation, the relative risk of postOLT mortality is increased by an average of about 150%. Finally, an analysis of patient survival in adult patients undergoing OLT for all non-FHF indications demonstrates that this risk stratification schema may be of use in estimating the 5-year postOLT survival of all patients undergoing OLT for any indication.

Three studies have previously examined the relationship between liver transplant recipient obesity and postOLT outcomes. The earliest of these studies included only 18 obese patients, and no significant postOLT survival difference was found between these patients and the non-obese controls (*12*). A second single-center study of 40 patients examined patient mortality, graft failure, posttransplant hospital length-of-stay, cardiovascular or wound complications and found no increase in incidence in liver transplant recipients with a BMI greater than 30 kg/m^2 (*13*). The most recent study to examine the relationship between recipient obesity and postOLT outcome included 64 nonobese, 36 obese patients (BMI between 27.8 and 31.1 kg/m^2 for men and between 27.1 and 32.3 kg/m^2 for women) and 21 severely obese (BMI ≥31.1 kg/m^2 for men and ≥32.3 kg/m^2 for women) patients undergoing OLT. Although no significant patient or graft survival difference was found, the posttransplant length of hospital stay, the total hospital cost of transplantation and the total incidence of perioperative complications were higher among the super obese recipients (*14*). The current study differs from these previous studies in many important ways. First, we adopted the World Health Organization definition of obesity as a BMI ≥30kg/m^2 (*8*). Although we focused only on adult patients undergoing OLT for FHF, the number of

patients analyzed in this study exceeds the number included in any previous study. In addition, these previous studies studied patients who underwent transplantation at a single institution, while the current study examines outcomes of recipients from multiple institutions. Finally, the current study is the first to verify recipient obesity as an independent risk factor for postOLT mortality through a multivariate analysis.

An elevated serum creatinine has been identified as being among the most important and consistent predictors of poor outcome after OLT for FHF (*4*, *6*, *7*, *9*). Many of these studies examined pretransplant serum creatinine as a continuous variable (*4*, *7*, *15*). Farmer et al. (*6*), presenting from a multivariate analysis of patients undergoing OLT for FHF, identified a serum creatinine concentration of 1.45 mg/dL as a critical threshold. When serum creatinine was >1.45 mg/dL and the time from onset of jaundice to onset of encephalopathy was more than 3.5 days, patient survival decreased to 50% compared to >80% survival in patients in which none of these criteria were present. We chose to adopt the serum creatinine threshold of 2 mg/dL in examining the relationship between serum creatinine and postOLT mortality, as this threshold had previously been demonstrated as a highly-influential predictor of postOLT mortality in a large single-institution review (*9*). Our results support the previous findings that an elevated serum creatinine as one of the most important predictor of poor outcome after OLT for FHF.

Farmer et al. previously noted that age was inversely correlated with probability of patient survival in a univariate survival analysis. This correlation did not reach statistical significance on a multivariate analysis, perhaps due to a small sample size. The authors noted an exception to this correlation, with age <1 year old being associated with a poor outcome, a finding consistent with other reports (*16*). We used a threshold of 50 years of age, a limit previously used by many transplant centers in considering patients for OLT (*10*), when examining this variable as a predictor of postOLT mortality in patients with FHF. We found that patients >50 years of age with FHF had a 39% higher rate of postOLT mortality than patients ≤50 years old.

A history of life support (defined in the UNOS database as including mechanical ventilation, vasopressors, intraaortic balloon pump, extracorporeal membrane oxygenation or prostaglandin E infusion) at the time of transplant registration was also highly predictive of postOLT mortality. Mechanical ventilation prior to transplantation has previously been identified as a risk factor for postOLT mortality. Farmer et al., focusing on patients undergoing OLT for FHF, identified history of preOLT hemodialysis as an independent risk factor for postOLT mortality. Indeed, patients who had undergone preOLT hemodialysis had a mortality rate 2.5 times higher than patients who had not undergone preOLT hemodialysis ($P=0.049$). A trend was seen in a univariate analysis of preOLT mechanical ventilation and postOLT survival; this did not reach statistical significance, however. In the current study, a history of life support was found to be an independent predictor of postOLT mortality. The differences in the findings of this study and previous studies are likely related to the larger number of patients examined in this series and the variable classification of "life support."

In creating this model we chose a point-system over a regression equation. Although a regression equation may improve the accuracy of prediction for postOLT survival, regression equations typically involve calculations with natural logarithms and therefore are inconvenient for clinicians to calculate at the bedside or in the ward. The risk-stratification scoring system proposed, on the other hand, is simple to calculate and interpret. The four variables needed are readily available to the clinician at the time of admission. Although the additional risks posed by BMI≥30 kg/m^2, creatinine >2 mg/dL, age >50 years old and history of life support are not exactly the same, they are so similar that making these risk factors equivalent in the scoring system does not compromise accuracy of the model greatly.

Finally, it is notable that even patients with the maximum score of four points (i.e. the highest-risk patients) had a 5-year postOLT survival of 42%. Two conclusions may be drawn from this. First, no combination of the clinical parameters examined in this study could predict postOLT patient mortality with more certainty. This is most likely because the this study was limited to patients deemed suitable candidates for transplantation. As such, presumably few of the patients in this study had any of the absolute contraindications to OLT for FHF such as active sepsis, cardiovascular insufficiency, respiratory failure, or pupils that are fixed and dilated for >2 hours. The fact that the patients included in this study have already undergone OLT signifies that their physicians very likely felt that they had a reasonable chance of meaningful recovery after transplantation, and therefore, were already partially risk-stratified. The patient population studied included only patients who underwent OLT for FHF. As a result this scoring system cannot be extrapolated to predicting survival of FHF patients receiving medical managament and should not be used in determining which FHF patients are appropriate candidates for OLT. Second, the fact that even the patients identified in this study as being at the highest risk for mortality after OLT achieved a 42% survival suggests that OLT is indeed indicated and, barring frank contraindications, is not a futile procedure in the setting of FHF.

In summary, four risk factors, readily available at the time of listing for transplantation, significantly affect patient survival in patients undergoing OLT for FHF. These include recipient age >50 years old, BMI of 30 kg/m^2 or greater, history of life support, serum creatinine concentration above 2.0 mg/dL. These risk factors can be used in a risk-stratification scoring system, in which patients at low risk for postOLT mortality can be distinguished from those at high risk for postOLT mortality. Such a risk-stratification scoring system could aid the clinician in estimating posttransplant survival for patients undergoing OLT for FHF.

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