Graft Survival and its Determinants: A 3 Year National Experience with Liver Transplantation in Israel

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Abstract

Background: There is a dearth of organs for liver transplantation in Israel. Enhancing our understanding of factors affecting graft survival in this country could help optimize the results of the transplant operation.

Objectives: To report 3 years national experience with orthotopic liver transplantation, and to evaluate patient and perioperative risk factors that could affect 1 year graft survival.

Methods: The study related to all 124 isolated adult liver transplantations performed in Israel between October 1997 and October 2000. Data were abstracted from the medical records. One-year graft survival was described using the Kaplan-Meier survival curve and three multivariate logistic regression models were performed: one with preoperative case-mix factors alone, and the other two with the addition of donor and operative factors respectively.

Results: Of the 124 liver transplantations performed, 32 failed (25.8%). The 1 year survival was lower than rates reported from both the United States and Europe but the difference was not significant. Of the preoperative risk factors, recipient age ≥ 60 years, critical condition prior to surgery, high serum bilirubin and serum hemoglobin ≤ 10 g/dl were independently associated with graft failure, adjusting for all the other factors that entered the logistic regression equation. Extending the model to include donor and operative factors raised the C-statistic from 0.79 to 0.87. Donor age ≥ 40, cold ischemic time > 10 hours and a prolonged operation (> 10 hours) were the additional predictors for graft survival. A MELD score of over 18 was associated with a sixfold increased risk for graft failure (odds ratio = 6.5, $P = 0.001$).

Conclusions: Graft survival in Israel is slightly lower than that reported from the U.S. and Europe. Adding donor and operative factors to recipient characteristics significantly increased our understanding of 1 year survival of liver grafts.

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Orthotopic liver transplantation has become the treatment of choice for patients with end-stage liver disease since 1983 [1]. In recent years the number of patients listed for OLT has grown, but the number of cadaveric donors has remained nearly constant, causing a dearth of organs for transplantation. This situation is especially true in Israel, which has a population of 6.5 million and is not a member of the European pool. Lack of organs is an added incentive to the need to understand what factors determine success or failure after OLT. One-year survival of the graft is a common criterion to evaluate success, usually adjusting for the preoperative risk profile of the patient prior to transplantation [2-5]. However, what happens after entry into the operating room is rarely measured in most studies, suggesting that quantification of risk associated with patient management is beyond the scope of observational studies. While recognizing that the surgical technique is hard to quantify and data on the operation hard to obtain, there is evidence from the literature that these factors are important for the outcome of the surgery [6]. Such 'process' risk factors, like complications during surgery and low quality of the graft, have been shown to be associated with graft survival [2-5].

We utilized the full cooperation of the transplant medical centers in Israel, which allowed us access to hospital medical records and operation reports, in our attempt to explore factors affecting graft outcome beyond the preoperative risk. Thus, the main objective of our study was to describe the national experience of liver transplantations in Israel over 3 years and to evaluate the respective roles of preoperative, donor and operative factors in graft survival.

Several recent studies have used the MELD scoring system (Model for End-Stage Liver Disease) to evaluate post-liver transplant patient survival, despite the fact that this system was derived from a model evaluating survival of patients on the waiting list [7-9]. These studies showed that patients with a high score prior to transplantation had a high mortality after OLT [10-15]. We therefore decided to include both the MELD and the CHILD (Child-Turcotte-Pugh) scores of the Israeli post-transplant patients as a sub-analysis.

Materials and Methods

During the period October 1997 to October 2000, 124 isolated adult liver transplantations were performed in Israel, with 32

OLT = orthotopic liver transplantation

MELD = Model for End-Stage Liver Disease

failures within 1 year. Of the 124 patients, 52 were operated in one of the three transplant centers and 43 and 29 were operated in the other two centers. During the study period a national waiting list for liver transplantation had not yet been instituted in Israel. Individual hospital lists were compiled by the clinical team and donated livers were allocated to the hospitals, in turn, by the National Center of Transplantation.

Data on the 124 liver transplantations were obtained by abstracting the medical records in each of the transplant centers by trained nurses, usually from the transplant unit itself. Surgeons heading these units aided the nurses when necessary. Data on donors were obtained from the National Center of Transplantation. Data included preoperative factors up to 6 months prior to transplantation, donor characteristics, and operative information. Deaths were ascertained within 1 year after OLT by linkage to the National Population Registry regardless of hospital discharge. Graft failure was defined as re-transplantation or death from any cause within 1 year of OLT.

Statistical analysis

The probability of graft survival over time using Kaplan-Meier curves was evaluated and compared for subgroups by Log Rank tests. To compare the crude graft survival among Israeli patients to the rates of the United Network for Organ Sharing and the European registry, the 95% point-wise confidence interval around the Israeli curve was calculated and the European and United States curves were drawn [Figure 1]. Comparisons of the transplanted patients in Israel vs. the USA and Europe were also made on frequencies of various characteristics. It was decided to evaluate our data using CHILD and MELD scores as well as our own model. For the MELD score the UNOS formula was applied to each patient and the score was formed. For the CHILD scores the appropriate five variables were combined to form the score.

The net effect of specific risk factors on graft survival controlling for all the other factors that entered the regression equation was estimated using logistic regression models. Three risk models were constructed. The first included the preoperative recipient characteristics, in the second we added donor variables, and in the third model we also added operative variables. The missing values for putative risk factors were included in the reference groups. Variables were entered using the forward method with statistically significant association determined as $P < 0.1$. The C-statistic of the model was calculated.

The Israeli case-mix logistic model and the MELD and CHILD scores were compared for their ability to predict graft survival within 1 year among the Israeli patients. The area under the ROC curve (C-statistic) was calculated for each of the models.

Results

Data on 124 transplantations in 114 patients are included in this report. Thirty-two graft failures occurred during the first year after transplantation: 10 of the failed patients required re-transplantation and 22 died during the follow-up period without undergoing re-transplantation.

The Israeli graft survival was compared to that from UNOS and Europe, presented in Figure 1. The cumulative 1 year graft survival in Israeli patients was 74% compared to 79.4% reported by UNOS [16], and 78% reported by the Europeans [17] for a parallel study period. Both the UNOS and the European curves fell within the 95% confidence interval of the Israeli curve. Comparison of patients' characteristics in Israel vs. the U.S. and Europe revealed that the Israeli patients tended to have more cholestatic liver cirrhosis and less fulminant hepatic failure as their primary diagnosis than their American and European counterparts. There were also fewer alchoholic cirrhosis cases among the Israeli transplanted population (6.5%), and most of the non-cholestatic cirrhosis cases were infectious in origin. However, these numbers could not be compared to the U.S. and European populations because of their grouping of all non-cholestatic cirrhosis patients together. The proportion of patients aged 65 and over in the Israeli transplanted population was lower than that of the U.S. transplanted patients (8.1% vs. 14.9% respectively).

The association of specific potential risk factors with 1 year liver failure in univariate analysis is presented in Table 1. The table is stratified by recipient characteristics appearing first, followed by donor and operative variables. The average recipient age was 48 years, with 20% (25 patients) over 60, of whom half were over 65. There was a male predominance, with 62% males vs. 38% females. The primary diagnosis among the recipients

CHILD = Child-Turcotte-Pugh
UNOS = United Network for Organ Sharing

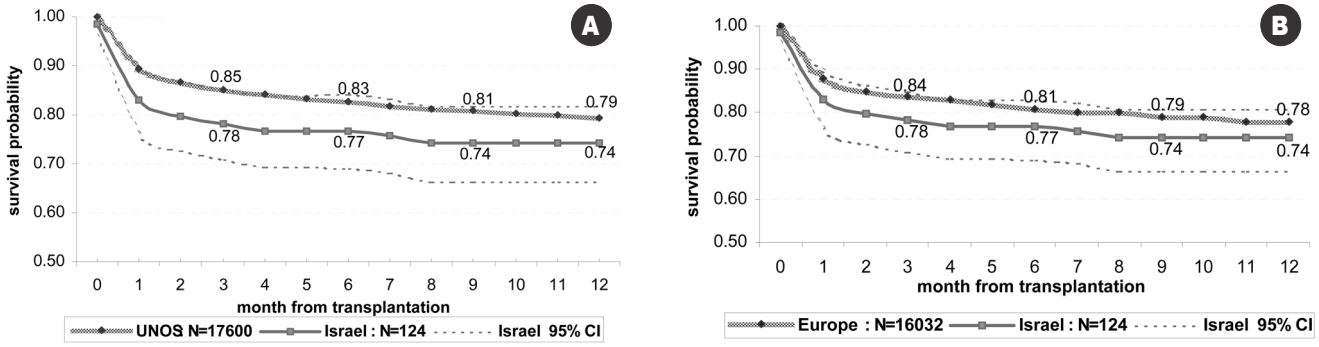

Figure 1. Kaplan Meier estimate for 1 year graft survival: Israel vs. **[A]** United Network for Organ Sharing [17] and **[B]** Europe [18]

Table 1. Univariate analysis of selected risk factors for 1 year graft survival after liver transplantation in Israel

Risk factor[1]	No.	% failures	Odds ratio	*P* (χ^2)
Preoperative variables				
Critical status 72 hrs prior to transplant[2]				
Yes	27	51.9	4.72	< 0.001
No	97	18.6	1.00	
Recipient's blood type				
O	36	44.4	4.07	0.003
B	21	23.8	1.59	0.446
A	59	17.0	1.00	
AB	(7)	(14.3)		
Recipient's age				
≥ 60 yrs	25	48.0	3.65	0.006
< 60 yrs	99	20.2	1.00	
Bilirubin [3,4]				
High	50	42.0	3.62	0.007
Medium	26	11.5	0.65	0.556
Low	48	16.7	1.00	
Hemoglobin[3]				
≤ 10 g/dl	30	40.0	2.16	0.083
> 10 g/dl	93	20.4	1.00	
Recipient's country of birth				
Asia/Africa	32	37.5	1.43	0.452
Europe/ America	38	10.5	0.28	0.036
Israel	51	27.5	1.00	
MELD score (tertiles)				
> 18	37	43.2	6.48	0.001
13–18	41	19.5	2.06	0.266
<13	38	10.5	1.00	
Primary diagnosis				
Primary sclerosing cholangitis[5], primary biliary cirrhosis	33	33.3	2.25	0.129
Hepatitis B and C viruses	66	18.2	1.00	
Alcoholic	(8)	(50.0)		
Malignancies	(1)	(100.0)		
Fulminant hepatic failure	(7)	(42.8)		
Other	(9)	(11.1)		
Previous liver transplant				
Yes	(12)	(58.3)	(3.30)	0.053
No	112	22.3	1.00	
Upper abdominal operation (except transplant)				
Yes	(16)	(50.0)	(3.25)	0.033
No	102	23.5	1.00	
Donor variables				
Cold ischemic time				
≥ 10 hrs	51	33.3	1.93	0.11
< 10 hrs	73	20.5	1.00	
Donor age				
≥ 60 yrs	(17)	(35.3)	(3.09)	0.07
40–59 yrs	47	34.0	3.21	0.01
≤ 39 yrs	57	15.8	1.00	
Organ damage discovered while harvesting				
Yes	(8)	(37.5)	(2.38)	0.03
No	99	20.2	1.00	
Donor's gender				
Female	47	31.9	1.62	0.24
Male	76	22.4	1.00	
Cause of death				
Other than trauma[6]	76	30.3	1.88	0.15
Trauma	48	18.7	1.00	
Donor infection[7]				
Yes	(10)	(20.0)	0.68	0.64
No	109	26.6	1.00	
Blood chemistry				
Serum sodium				
> 146	44	22.7	0.83	0.82
136–146	61	26.2	1.00	
< 136	(12)	(16.7)		
Serum creatinine				
> 1.3	(15)	26.7	1.06	0.92
≤ 1.3	106	25.5	1.00	
Creatine phosphokinase				
> 320	34	17.6	0.62	0.58
≤ 320	43	25.6	1.00	
Lactate dehydrogenase				
> 200	74	22.9		
≤ 200	(16)	(31.2)		
Blood urea nitrogen				
> 18	52	30.7	1.77	0.20
≤ 18	65	20.0	1.00	
Aspartate aminotransferase				
> 40	37	27.0	1.28	0.64
≤ 40	76	22.4	1.00	
Alanine aminotransferase				
> 56	(16)	(12.5)		
≤ 56	89	25.4		
Viral infection[8]				
Any viral infection	80	26.2	1.06	0.88
No viral infection	44	25.0	1.00	
Operative variables				
Duration of surgery				
≥ 10 hrs	30	43.3	3.02	0.013
< 10 hrs	94	20.2	1.00	
Complications during the surgery (mainly bleeding)				
Yes	28	39.3	2.28	0.06
No	98	22.1	1.00	
Blood transfusion during operation (no. of blood portions)				
22+	59	27.1	2.32	0.3
9–21	31	32.3	3.36	
1–8	29	13.8	1.00	
Biliary anastomosis				
Roux-en-y hepatico jejunostomy	(18)	(33.3)	(1.71)	
Duct to duct with T-drain	67	23.9	1.07	
Duct to duct without T-drain	31	22.6	1.00	
Vein anastomosis				
Cavocavostomy	(17)	(35.3)	(1.75)	
End-to-end	62	24.2	1.03	
Piggy back	38	23.7	1.00	

[1] No. of patients totaling less than 124 is due to missing data.
[2] Any of the following: mechanical ventilation, hospitalization in ICU or dialysis.
[3] The closest available blood test prior to surgery.
[4] High bilirubin = > 3 µmol/L for non-cholestatic disease or > 10 µmol/L for cholestatic disease, medium bilirubin = 2–3 µmol/L, and low bilirubin = < 2 µmol/L.
[5] Rates based on a denominator < 20
[6] Tumors, stroke, aneurysm, myocardial infarction.
[7] Pneumonia, urinary tract infection, sepsis.
[8] Anti-hepatitis C virus, anti-human immunodeficiency virus, HbsAg, anti-cytomegalovirus.

was hepatitis (66 patients, 53.2%), and only 8 patients had alcoholic liver failure. An additional 26.6% were diagnosed as primary biliary cirrhosis and primary sclerosing cholangitis. There was only one patient with hepatic carcinoma and seven with acute fulminant hepatic failure. Another factor, body mass index, considered important in the USA, could not be evaluated in this data set because only two of the recipients had a BMI above 35. The average BMI for our recepient population was 25.5 (range 16.1–36.1). The preoperative screening of recipients' putative risk factors revealed that nine had a significant association with graft failure ($P < 0.1$): i.e., critical status 72 hours prior to transplantation, recipient blood type O, recipient age ≥ 60, high serum bilirubin > 3, low hemoglobin (≤ 10 g/dl), and being immigrants from Asia/Africa. The mean MELD score for the entire Israeli transplanted population was 16.2 ± 7.5, and a high MELD score (> 18) had a significant association with graft failure ($P < 0.01$). Previous liver transplantation and previous upper abdominal surgery were also significantly associated with graft failure, but the numbers were small.

Risk factors among donors [Table 1] included age over 40 in over half of them (n=67), and age and cold ischemic time (over 10 hours) were significantly associated with graft failure. Other donor characteristics – such as gender, cause of death, bacterial infections prior to death, blood biochemistry and viral profile – were not associated with graft failure ($P < 0.1$). Organ damage discovered while harvesting [Table 1] was observed in only a few livers (6%, 8 donors) and they were therefore not included later in the model. Of the eight donated livers, three were reported as damaged during the harvesting operation, while the rest were found to be 'less than opitmal organs' during the operation because of a tumor, anatomic aberration, etc.

Among the operative risk factors [Table 1], duration of surgery over 10 hours (30 patients) meant graft failure in 43.3% (mean duration of surgery for the entire group was 8.9 hours). Among these patients more than 40% reported surgical complications. Other operative factors – biliary anastomoses, vascular anastomoses, and number of blood transfusions during surgery – did not show a significant association with graft failure. Of the total sample, 82.5% were duct-to-duct anastomoses with or without T-drains, 97.5% were end-to-end portal anastomoses and 92.5% hepatic-celiac anastomoses. Of the vein anastomoses 52.5% were end-to-end and 32.2% were piggyback.

Of the 32 graft failures, 18.7% were diagnosed as primary non-function, nearly half (43.7%) were due to postoperative infection, 18.8% were due to blood vessels occlusion and 15.7% to cardiovascular diseases.

Patients who survived graft failure to be eligible for a second transplantation varied in most characteristics, with their CHILD score between B and C and their MELD score between 5.1 and 29.1. Among these patients postoperative infections were the most common complication.

The three logistic models for factors associated independently with graft failure are presented in Table 2. The first model included case-mix factors alone: Recipient age ≥ 60 years (odds ratio = 4.93), critical condition prior to transplantation (OR = 3.41), preoperative low hemoglobin ≤ 10 g/dl (OR = 2.29) and high serum bilirubin (OR = 4.10) were all statistically significant. The C-statistic of this model was 0.79. In the second model, donor characteristics were added to the previous factors. The significant added factors were: donor age ≥ 40 years (OR = 2.21) and cold ischemic time > 10 hours (OR = 3.23). The C-statistic of this model was 0.84. In the last model, operative factors were also added. The significant addition at this stage of the analysis was duration of surgery ≥ 10 hours (OR = 6.82). The C-statistic of the last model was 0.87.

Table 2. Three multivariate logistic models for 1 year graft survival after liver transplantation: preoperative, preoperative + donor, preoperative + donor + operative factors

	Model 1 Preoperative variables only		Model 2 Preoperative and donor variables		Model 3 Preoperative, donor and operative variables	
Risk factor	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Recipient age ≥ 60 yrs	4.93	< 0.001	4.59	< 0.001	4.90	0.01
Critical status 72 hrs prior to transplant*	3.41	0.02	5.33	<0.001	5.00	0.01
Bilirubin prior to transplant**						
High	4.10	0.01	3.02	0.06	4.49	0.02
Medium	1.34	0.71	1.18	0.83	1.31	0.75
Hemoglobin prior to transplant ≤ 10 g/dl	2.29	0.10	2.89	0.05	3.86	0.02
Donor age ≥ 40 yrs	–	–	2.21	0.14	3.67	0.03
Cold ischemic time >10 hr	–	–	3.23	0.02	3.36	0.03
Duration of surgery ≥10 hr	–	–	–	–	6.82	<0.001
C-statistic	0.79		0.84		0.87	

* Any of the following: mechanical ventilation, hospitalization in ICU or dialysis.

** High bilirubin = > 3 µmol/L for non-cholestatic disease or > 10 µmol/L for cholestatic disease, medium bilirubin = 2–3 µmol/L, amd low bilirubin < 2 µmol/L.

While these three models were based on the Israeli data we compared the C-statistics of our first model to the C-statistics of the MELD score and CHILD score applied to our population. The 1 year graft failure was better predicted by the MELD score model than the CHILD, with a C-statistic of 0.70 vs. 0.65 for the CHILD respectively.

A sub-analysis of the association between graft failure and the combined effect of recipient and donor ages [Figure 2] revealed that while no multiplicative interaction could be detected within the logistic model, the 'old to old' combination (donor age ≥ 40 to recipient age ≥ 60) had a marked additive effect and was associated with an extremely high failure rate. The graft survival

BMI = body mass index

OR = odds ratio

in this group was only 44%, in contrast to a 73% survival rate among patients with only one being 'old' – either the recipient or the donor. This was also in marked contrast to the survival of 86% when both recipient and donor were 'young'.

Discussion

Our sample, although small, represents the experience of the entire country with liver transplantations within 3 years. The crude 1 year graft survival in Israel was lower than that reported by Europe and the U.S. for the same period [16,17]. The scarcity of organs for transplant could affect the outcome because of the more frequent utilization of older donors and less than perfect organs [Table 1, Figure 2]. Our analysis supports this hypothesis as the extremely high failure rate (56%) occurred among older patients transplanted with older livers. The observed 1 year graft failure for 'young' recipients transplanted with 'young' donor' livers was 14%, a fourfold reduction. Markmann et al. [18] discuss the 'old to old' allocation as a problematic practice. They show a significant association with graft failure of aged recipients and separately of aged donors, but they did not have a combined effect of 'old to old' allocation, probably because this practice is rare. In our data the 'young to old' transplantations had failure rates of 27%, half the rate for 'old to old'.

Three logistic models were constructed to evaluate the independent association between graft failure and patient inherent characteristics (case-mix factors) in the first model, donor factors added in the second, and operative risk factors included also in the third model. As expected, the addition of donor and operative factors increased the explanatory power of the models (C-statistic rose from 0.79 in the first model to 0.87 in the third). However, it is clear that the small numbers in this study precluded a more detailed evaluation of the causes of failure and operative complications. For example, suboptimal organs and complications during the surgical procedure that had an association with graft failure in our data set did not appear in the logistic models, probably because of their relative rarity. However, our case-mix model agrees with other published reports [2-5,18,19] and was similar to the most significant factors in a model developed by Thuluvath and colleagues [19] of 38,876 liver transplantations. They found that, in their model, critical status prior to transplant, old recipients and high serum bilirubin were highly significant factors. Critical status 72 hours prior to transplantation is a known risk factor and a common finding in many studies (in our model OR = 3.41). It is a composite parameter, including recipients who were hospitalized in the intensive care unit, needed mechanical ventilation, or required hemodialysis prior to the operation. In other studies the effect of each of these variables could be examined separately [2,18]. High serum bilirubin (in our model OR = 4.1) was also a common finding in many studies and is one of the components of the MELD score. However, the low hemoglobin that we found to be an independent risk factor for failure is not a common risk factor in the literature; in fact, some clinicians prefer hemoglobin to be ≤ 10 because of the low coagulability, and an impression of a lower incidence of hepatic artery thrombosis. We cannot resolve this discrepancy. In our data the low hemoglobin was not associated with hypersplenism. It should be noted that low hemoglobin postoperatively was an observed risk factor for mortality in other surgical procedures as well [6]. Other factors reported by Thuluvath et al. [19] that did not agree with our findings were high BMI, which in our sample was very rare (only two patients had BMI over 35), and malignancy or hemochromatosis as the etiology of the liver failure applied to only one patient in our sample. Although Thuluvath's team evaluated 17 separate etiologies for liver failure, 86.3% of our sample had chronic viral infection, alcoholic cirrhosis, or cryptogenic cirrhosis, all fitting one group in Thuluvath's report (group 3) [19].

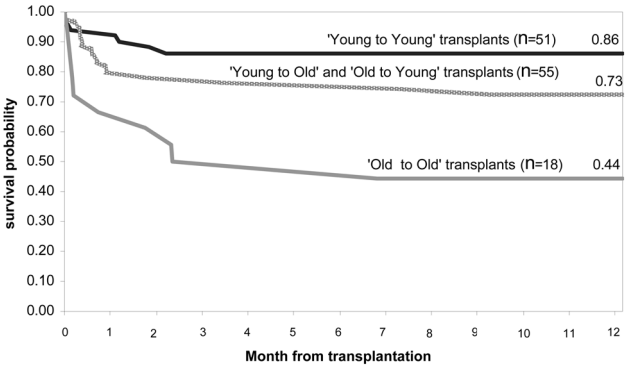

Figure 2. Kaplan Meier survival after liver transplantation up to 1 year by age of recipient and age of donor.
Log Rank 'Young to Young' vs. 'Old to Old' = 0.0001
Log Rank 'Young to Old' and 'Old to Young' vs. 'Old to Old' = 0.0076

Of all the donor factors studied, only high age and prolonged cold ischemic time added significantly to the risk for graft failure (second model). These factors were also found to be significant in other studies either in a univariate or in multivariate analyses [2,3,18,19]. The special importance of prolonged cold ischemic time (over 10 hours) is that it is amenable to intervention – in a small country like Israel. A long operation was a strong addition to the risk of failure in the third model. This was a proxy variable for complications during the operation. Half the patients with prolonged operations had reported complications during the procedure, which is probably an under-reporting.

The comparison between our first model and the preoperative MELD [10-15] and CHILD scores was performed because of the wide use of these scores both for allocation and for evaluation of liver failures post-transplantation. The MELD score was also found to be a good predictor of graft survival [2,11,12]. The average MELD score for our entire sample was 16.2, identical to the average score in American patients [11,12]. Comparing the MELD and CHILD scores to our first model was done using the ROC curves for the three models. It showed that both the MELD and CHILD scores performed moderately well on our data, with the area under the ROC curves being 0.7 and 0.65 respectively, but our case-mix model had a higher C-statistic, 0.79.

The main limitation of this report is the small number of transplants performed in Israel. The lack of a large pool of donors is probably responsible for both the small overall number

of transplantations performed and the use of less than optimal organs.

In conclusion, the addition of donor and operative factors to the models of graft failure is important: it gives clinicians a perspective that will help improve the outcome of transplantations under conditions of a severe shortage of organs.

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