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Michel van Agthoven
Herold J. Metselaar
Hugo W. Tilanus
Rob A. de Man
Jan N. M. IJzermans
B. Martin van Ineveld

A comparison of the costs and effects of liver transplantation for acute and for chronic liver failure

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M. van Agthoven (✉) · B. M. van Ineveld
Department of Medical Technology Assessment, Erasmus University Medical Centre, P. O. Box 1738,
3000 DR Rotterdam, The Netherlands
e-mail: vanagthoven@bmg.eur.nl
Tel.: + 31-10408-8574
Fax: + 31-10408-9094

H. J. Metselaar · R. A. de Man
Department of Hepatogastroenterology, Erasmus University Medical Centre, P. O. Box 1738, 3000 DR Rotterdam, The Netherlands

H. W. Tilanus · J. N. M. IJzermans
Department of Surgery, Erasmus University Medical Centre, P. O. Box 1738, 3000 DR Rotterdam, The Netherlands

Abstract Little is known about costs and cost-effectiveness of liver transplantation (LTx) for acute liver failure compared to costs and cost-effectiveness of LTx for chronic liver failure. In this study, costs of acute and of chronic LTx patients were determined in a retrospective study. Files of 100 consecutive patients who underwent LTx in 1993–1997 were studied. Costs up to 1 year after LTx were Euro 107,675 (chronic liver failure) and Euro 90,792 (acute liver failure). The difference was mainly caused by higher hospitalisation costs and higher personnel costs for chronic liver failure. Medication costs for acute liver failure were higher, due to a high administration rate of expensive anti-HBs immunoglobulin therapy in patients with viral hepatitis B. LTx for chronic liver failure is more costly and seems to be more cost-effective than LTx for acute liver failure, since 1-year survival is higher in patients who underwent transplantation for chronic liver failure.

Keywords Liver transplantation · Cost analysis · Survival · Acute liver failure · Chronic liver failure

Introduction

Liver transplantation (LTx) is nowadays considered to be an established treatment for end-stage liver disease. In the Erasmus University Medical Centre Rotterdam (EMCR), a LTx program was started in 1986. In 1988, a cost analysis of the first Dutch LTx program which was started in the University Hospital Groningen showed average costs of Euro 111,150 [21] per patient (corrected for inflation). In the Netherlands, separate governmental financing systems exist for this kind of highly specialised medical treatment. The annual number of transplantations is therefore fixed in advance by individual hospitals, in the light of the incoming reimbursements on the one hand, and the insufficient knowledge of the mentioned average costs of Euro 111,150 for each patient undergoing transplantation on the other hand. However, this amount was determined more than ten years ago in a cost analysis which was particularly tailored to LTx for chronic liver failure. As the EMCR advocates LTx for acute liver failure, it performs relatively more and more transplantations for acute patients each year. In order to be able to continue this policy in spite of budgetary constraints, it was desirable to gain insight into the average costs of LTx for acute liver failure compared to the average costs of LTx for chronic liver failure. Although it is known that LTx for chronic liver failure still leads to higher survival rates compared to LTx for acute liver failure [6], the economical consequences of operating relatively more acute patients

Table 1 Patient characteristics from 100 consecutive patients who underwent LTx in the EMCR from January 1993 to November 1997

Patient characteristics		
Number of patients		100
Male		56
Female		44
Median age all patients (range)		46 (16–66)
Median age patients with chronic liver failure (range)		49 (23–66)
Median age patients with acute liver failure (range)		36 (16–59)
Number of retransplantations		9
Number of patients with chronic liver failure as primary diagnosis for LTx		75
of which:	Primary sclerosing cholangitis, primary billiary cirrhosis	30
	Cryptogenic cirrhosis, post-alcoholic cirrhosis, viral cirrhosis (B, C)	34
	Metabolic disorders	5
	Hepatocellular carcinoma	3
	Unknown	3
Number of patients with acute liver failure as primary diagnosis for LTx		25
of which:	Acute viral disease (Hep B, Hep E, EBV)	6
	Acute liver failure due to toxicity or medication	4
	Acute liver failure due to Wilson's disease	3
	Unknown	12

have never been assessed. Therefore, we conducted a retrospective analysis of costs and effects attained by patients who underwent orthotopic LTx between 1993 and 1997. In this analysis we distinguished between costs of LTx for acute liver failure and those of LTx for chronic liver failure. As the budgetary negotiations are focused annually, costs and effects were assessed up to 1 year post transplantation. Within this time interval, we assumed to have assessed the majority of the total costs per patient, as the costs for this kind of intervention are known to be particularly made "up front".

Materials and methods

This cost analysis was based on a detailed review of all patient files and records in the hospital information system from 100 consecutive patients who underwent orthotopic LTx in the EMCR from January 1993 to November 1997. All medical procedures, diagnostic tests, hospital days, consultations, administered drugs and blood components from each of these patients were stored in a database.

In contrast to charges, cost prices are the best guide for the theoretically proper opportunity costs [14]. Therefore, we determined so called "integral" unit prices for the most important cost items, which reflects real resource use, including a raise for overhead costs [30]. To determine the use of resources, we followed the micro-costing method, which is based on a detailed inventory and measurement of resources consumed [19]. The valuation of the resources and overhead costs was based on financial data from the EMCR's financial department (1996 level, 1 Euro = 2.20371 Dutch Guilders). The contents of the overhead costs (which primarily determine costs of hospital days) were thoroughly checked to prevent double-counting costs that were already recorded. Expert opinion was followed to determine costs of disposables used during LTx and personnel activities on behalf of LTx patients. Personnel costs contain the costs of all specialists and employees who have been specifically assigned to the LTx team (surgeon, hepatologist, anaesthetist, registrars, psychologist, nurses, nurse co-ordinator, operating room personnel, social worker, dietician, administration, datamanager and physiotherapist). Also accounted for are costs arising from patients who did not undergo transplantation after having been evaluated but were not accepted for LTx or who died while on the waiting list, and additional costs arising from patients who underwent retransplantation. The institutional perspective was taken, costs arising outside the hospital were not considered. Costs were determined up to one year after the date of each LTx. Because of this 1-year period, no discounting was applied. All costs are presented as average costs per patient. Dutch survival data were provided by Eurotransplant and concern all 316 patients older than 16 years who underwent an orthotopic non-split LTx in the Netherlands between January 1990 and December 1996.

Results

Patients

The characteristics of the assessed 100 patients are presented in Table I. There was a significant age difference between patients who underwent transplantation for chronic liver failure (49) and patients who underwent transplantation for acute liver failure (36; $P = .000$).

Costs before LTx

Patients with chronic liver failure were extensively evaluated to assess suitability for transplantation. This clinical evaluation took 26 days on average, which caused a higher number of hospital days before LTx in chronic patients (Table II). Patients with acute liver failure were only hospitalised for 2 days in the Intensive Care ward before the LTx was performed. Due to the clinical

Table 2 Hospital days (mean, median, range) in different phases of treatment up to 1 year after LTx and total hospitalization costs

Treatment phase	Ward	All patients	Chronic liver failure	Acute liver failure
Before LTx	General	21 (23;0–112)	26 (24;2–112)	0 (0;0–7)
	Intensive care	0 (2;0–9)	0 (0;0–4)	2 (2;1–9)
LTx to 1st discharge	Intensive care	16 (6;1–273)	15 (5;1–273)	18 (7;1–83)
	General	31 (21;0–186)	33 (21;0–186)	25 (30;0–47)
Readmissions	General	13 (12;0–87)	15 (12;0–87)	8 (10;0–21)
Total no. of days		81 (61;2–379)	90 (69;21–379)	54 (44;2–158)
Total costs		Euro 17,425	Euro 18,401	Euro 14,499

Table 3 Total average costs (Euros) per patient up to 1 year after LTx, distinguished to patients with chronic liver failure and patients with acute liver failure

Cost component	All patients	Chronic liver failure	Acute liver failure
Before LTx			
Hospitalization	3,433 (3.3%)	4,233 (3.9%)	1,210 (1.3%)
Diagnostic procedures/tests	250 (0.2%)	310 (0.3%)	70 (0.1%)
Medication	64 (0.1%)	76 (0.1%)	19 (0.0%)
Consultations/outpatient visits	538 (0.5%)	723 (0.7%)	36 (0.0%)
Personnel	9,737 (9.4%)	12,633 (11.7%)	1,044 (1.2%)
Patients not transplanted	7,816 (7.6%)	7,816 (7.3%)	7,816 (8.6%)
Costs before LTx	21,838 (21.1%)	25,791 (24.0%)	10,195 (11.3%)
From LTx up to 1 year after LTx			
Hospitalization	13,992 (13.5%)	14,168 (13.2%)	13,289 (14.8%)
Diagnostic procedures/tests	2,485 (2.4%)	2,378 (2.2%)	2,807 (3.1%)
Anti-HBs immunoglobulin	7,200 (7.0%)	6,940 (6.4%)	10,112 (11.2%)
Other medication	3,999 (3.8%)	3,232 (3.0%)	4,035 (4.5%)
Blood components	2,783 (2.9%)	2,941 (2.7%)	2,289 (2.5%)
Consultations/outpatient visits	2,429 (2.3%)	2,429 (2.3%)	2,429 (2.7%)
Personnel	30,386 (29.4%)	31,428 (29.2%)	27,268 (30.3%)
Surgery operating room	3,646 (3.5%)	3,646 (3.4%)	3,646 (4.0%)
Eurotransplant registration	5,569 (5.4%)	5,569 (5.2%)	5,569 (6.1%)
Additional surgical procedures	3,244 (3.1%)	3,244 (3.0%)	3,244 (3.6%)
Disposables on behalf of LTx	4,282 (4.1%)	4,282 (4.0%)	4,282 (4.7%)
Medical equipment on behalf of LTx	1,627 (1.6%)	1,627 (1.5%)	1,627 (1.8%)
Costs from LTx up to 1 year after LTx	81,642 (78.9%)	81,884 (76.0%)	80,597 (89.6%)
Total costs	103,480 (100%)	107,675 (100%)	90,792 (100%)

evaluation, all other costs (diagnostics, medication, consultations and personnel) were also higher in patients with chronic liver failure. Next to the clinical evaluation, patients with chronic liver failure were seen 6 times at the LTx outpatient clinic before LTx. Personnel costs were assigned on the basis of the average number of days per patient spent and were therefore higher in chronic patients. The costs of patients who did not undergo transplantation after having been evaluated were also ascribed to the total costs per patient of this phase. During the assessed years, the costs of an annual number of 39.33 patients who were evaluated but did not undergo transplantation were divided among all patients who underwent transplantation. Their medical consumption during the evaluation was similar to patients who underwent transplantation afterwards.

In total, costs of patients with chronic liver failure were Euro 25,791 before LTx, compared to Euro 10,195 for patients with acute liver failure (Table III).

Costs from LTx up to 1 year after LTx

There was no significant difference in the number of hospital days from LTx to first discharge between patients with acute or such with chronic liver failure (Table II). The number of readmission days was higher in patients with chronic liver failure as a consequence of a higher 1-year survival in this group.

Immunosuppression after LTx was based on a triple-drug scheme (Cyclosporine, Azathioprine, Prednison) of which Cyclosporine accounted for 13% of the aver-

Table 4 Sensitivity analysis

Cost item	Decrease	Increase
Hospitalization: clinical evaluation	– Euro 743	+ Euro 0
Hospitalization: after LTx (up to discharge)	– Euro 593	+ Euro 0
Hospitalization: readmissions	– Euro 507	+ Euro 0
Medication (except anti-HBs immunoglobulin)	– Euro 203	+ Euro 0
Anti-Hbs immunoglobulin	– Euro 0	+ Euro 5,911
Operating room	– Euro 255	+ Euro 0
Patients not undergoing transplantation	– Euro 2,642	+ Euro 0
Total decrease/increase	– Euro 4,943	+ Euro 5,911

age medication costs (due to relatively high costs of the intravenous cyclosporine and high total administration dose of its oral variant). In total, medication costs for acute liver failure are Euro 3,975 higher than for chronic liver failure (Table III). First, a higher administration frequency of anti-CMV immunoglobulin was responsible for these higher costs (accounted for 12% of medication costs), but most of the difference was determined by a higher administration rate of anti-HBs immunoglobulin in patients with viral hepatitis B (Hepatect, Biotest, Dreieich, Germany). This immunoglobulin determined 64% of the overall average medication costs from LTx onwards, although it was administered in only 10% of the patient population. It was administered averagely 11 times per patient to 7 patients with chronic hepatitis B cirrhosis, and to 3 patients with acute hepatitis B. The costs of 11 administrations were Euro 73,881 per hepatitis B patient.

Costs of consultations up to 1 year after LTx were mainly constituted by an average number of 21 visits to the LTx outpatient clinic (16% of the mentioned amount was caused by consultations of other specialists). Personnel costs were in this phase also assigned on the basis of the number of days per patient spent, and were therefore again higher for chronic patients.

The lower part of Table III presents cost categories which were assumed to be the same for all patients, as they did not vary within their specific groups. In all of these amounts, a raise was calculated for additional costs of a possible retransplantation (8% chance in the assessed patient group). Costs of the surgery operating room were based on a total average occupation (including preparation) of 620 min. Costs of Eurotransplant contained costs of registration and extirpation of the donor organ. The costs of additional surgical procedures were constituted by the costs of relaparotomies (on average 0.83 per patient) and tracheotomies (0.15 per patient), which resulted in an additional 139 min occupation of the operating room per patient.

The total costs per patient from LTx onwards were the same for chronic patients (Euro 81,884) and acute patients (Euro 80,597). The higher anti-HBs immunoglobulin costs in the latter group were outweighed by the higher personnel costs in the former group. The total costs per patient, including the pre-transplantation costs, were higher for chronic patients (Euro 107,675 vs. Euro 90,792).

Sensitivity analysis

The drawback of retrospective analyses assessing a number of years is that changes beginning during the assessed time interval are not properly accounted for. Furthermore, if these changes are likely to sustain, the analysis does not give a representative view of the costs of the same intervention in the near future. We therefore applied a scenario analysis [14] to adapt the results of the analysis for observed and expected changes (Table IV).

No changes are expected in the way the LTx itself is performed, as the main changes have already emerged during the 1980's, when LTx was still in development. Only the duration of the LTx procedure slightly decreased during the assessed years. For the current scenario analysis, we assumed that the decrease in duration will sustain.

We observed a decrease in the number of hospital days during the pre-transplantation evaluation of the patients with chronic liver failure, in the number of hospital days from LTx up to first discharge, and in the number of readmission hospital days. The latter changes are caused by the tendency to transplant earlier, which has a favourable effect on recovery. For the current scenario analysis, the duration of the clinical evaluation before LTx in chronic patients is assumed to decrease from 26 to 22 days. This also affects the costs of patients who did not undergo transplantation after having been evaluated. The average number of hospital days from LTx to first discharge for all patients is assumed to decrease from 47 to 45, while the number of readmission days is expected to decline from 13 to 10. As a result of these lower numbers of hospital days, medication costs (except anti-HBs immunoglobulin) will also decrease.

A little change is expected in the composition of the annual patient group, as the proportion of "classical diagnoses" for LTx (PBC and PSC) is assumed to decrease in the near future, while the proportion of patients with viral hepatitis is expected to increase. Although this substitution turned out to have no influence

Table 5 Absolute costs per patient (Euros), and 1-year survival rates (+ number of patients) of Dutch patients transplanted between 1990–1996, and relative costs per patient

Diagnosis	Absolute costs per patient	Dutch 1-year survival (*n*)	Relative costs per patient
Patients with chronic liver failure	107,675	0.83 (248)	129,729
of which			
Primary sclerosing cholangitis, primary billiary cirrhosis	102,092	0.88 (91)	116,014
Cryptogenic cirrhosis, post-alcoholic cirrhosis, viral cirrhosis (B, C)	113,219	0.80 (120)	141,524
Metabolic disorders	115,590	0.91 (13)	127,022
Hepatocellular carcinoma	99,924	0.73 (15)	136,882
Unknown	107,328	0.89 (9)	120,832
Patients with acute liver failure	90,792	0.62 (68)	146,439
of which			
Acute viral disease (Hep B, Hep E, EBV)	132,005	0.73 (11)	180,829
Acute failure due to toxicity or medication	91,904	0.67 (9)	137,170
Acute failure due to Wilson's disease	97,104	0.83 (6)	116,993
Unknown	69,586	0.42 (26)	165,681

on hospitalization costs, it will lead to an augmentation of the costs of anti-HBs immunoglobulin. For the patients to whom the anti-HBs immunoglobulin were administered, the one-year treatment costs of this drug were Euro 73,881. If the future annual patient groups consist of 25 patients, the average anti-HBs costs per patient will be Euro 2955. According to the scenario analysis, an additional number of two additional anti-HBs immunoglobulin therapies is expected to be necessary.

No changes are observed or expected in the costs of diagnostic procedures, blood components, consultations, Eurotransplant registration, additional procedures, disposables, and medical equipment. Also, no changes are foreseen in the composition of the LTx team. We therefore assume to have calculated a representative amount for these cost categories.

The mentioned changes lead to an uncertainty margin of – Euro 4,943 to + Euro 5,911 around the calculated average costs per patient (Euro 103,480) (Table IV). However, the changes in the "decrease column" of Table IV have actually already been realised, while the change mentioned in the "increase column" is expected to come into effect in the near future. As these changes nearly compensate each other, we expect the calculated average costs per patient to be representative for future patients. In total, a rise of Euro 968 may be expected as a consequence of more patients undergoing transplantation for viral hepatitis.

Subgroup analysis and survival

The storage of all patient data in a database enabled us to specify costs of diagnostic groups (Table V). Costs of patients with acute viral disease (Euro 132,005) may appear to be high, but this can be explained by the relatively high number of patients with hepatitis B in this group (50 %), to whom anti-HBs immunoglobulin is administered. The costs of patients with acute viral disease are in accordance with the costs of other acute patients, when costs of anti-HBs are left out of consideration (Euro 84,636). The costs of patients with acute liver failure of unknown cause were low due to a low survival rate in this group (60 % died within 1 month after LTx).

A connection of these costs to 1-year survival rates of a cohort of 316 Dutch patients who were underwent transplantation between 1990 and 1996 yields a crude assessment of the cost-effectiveness of LTx in the various diagnosic groups (Table V). When the absolute 1-year costs are divided by these survival rates, the relative costs per patient show. This means that after one year, the costs made on behalf of the deceased patients within a diagnostic group are distributed over the patients that survived one year. From this analysis, LTx in patients with chronic liver failure seems to be more cost-effective than performing LTx in patients with acute liver failure.

Discussion

Liver transplantation (LTx) for patients with chronic liver disease is known to be an effective treatment for end-stage liver disease. Since the early 90s, LTx is being performed increasingly often in patients with acute liver failure. Little is known about costs and cost-effectiveness of LTx for acute liver failure compared to those for LTx for chronic liver failure. Our centre aims to distinguish itself with LTx for acute liver failure, but the annual number of patients is fixed in advance as a consequence of budgetary constraints. It was therefore desirable to gain insight in the cost patterns of LTx for acute liver failure, compared to cost patterns of the estab-

Table 6 Reported ranges of 1-year survival after LTx in different diagnostic groups compared with the overall Dutch 1-year survival rates

Indication	References	'International' median survival (range)	Dutch 1-year survival
Chronic liver failure:	6	0.84 (0.84)	0.83
PSC	1, 13, 20, 24, 27, 28, 29, 34, 39	0.88 (0.73–0.97)	
PBC	4, 13, 15, 34	0.81 (0.75–0.92)	
Total		0.85 (0.73–0.97)	0.88
Cryptogenic cirrhosis	2, 11, 13	0.75 (0.72–0.84)	
Post-alcohol cirrhosis	8, 12, 13, 15, 23, 32, 33	0.83 (0.73–0.96)	
Hepatitis B cirrhosis	12, 13, 26, 36	0.78 (0.53–0.93)	
Hepatitis C cirrhosis	2, 7, 10, 12, 13, 16, 18	0.83 (0.70–0.97)	
Total		0.83 (0.53–0.97)	0.80
Metabolic disorders	3, 12, 13, 15	0.83 (0.63–0.90)	0.91
Hepatocellular carcinoma	13, 14, 15, 17, 22, 31, 37	0.68 (0.47–0.82)	0.73
Acute liver failure:	6	0.64 (0.64)	0.62
Viral Hepatitis B	5, 36, 40	0.70 (0.41–0.72)	
Epstein-Barr virus	25	0.73 (0.73)	
Total		0.71 (0.41–0.73)	0.73
Toxicity/medication	5, 40	0.48 (0.33–0.63)	0.67
Wilson's disease	3	0.73 (0.73)	0.83
Unknown cause	5	0.69 (0.69)	0.42

lished LTx for chronic liver failure. We assessed 1-year costs of patients who underwent orthotopic LTx in our centre in the years 1993–1997. The main finding of this study is a difference of Euro 17,000 in favour of LTx for acute liver failure. The lower costs were mainly caused by a limited pretransplant evaluation of patients with acute liver failure and less readmissions (due to a lower 1-year survival). The difference in costs will be even more striking when patients with acute hepatitis B are excluded, due to the relatively high administration rate of an expensive anti-hepatitis surface immunoglobulin preparation (Hepatect, Biotest, Dreieich, Germany) in these patients. The connection of these costs to 1-year survival rates yielded an early impression of the cost-effectiveness of LTx in acute patients compared to the cost-effectiveness of LTx in chronic patients, which was in favour of the latter group.

The rationale for this measurement of cost-effectiveness is that the majority of costs of LTx patients arise within the first year and that survival in patients having survived one year seems to be excellent, irrespective of the original diagnosis (i. e. acute or chronic liver failure). In the Netherlands, there is no significant difference in 5-year survival between chronic patients (59%) and acute patients (62%, $P > .05$, data provided by Eurotransplant). Both our results in costs and effects are not supported by statistical differences. However, the overall cost results are in accordance with earlier results. The amount of Euro 103,480 is lower than the inflation corrected Euro 111,150 from the Dutch 1988-analysis [21], but this can probably be ascribed to learning effects. They are higher than the results of a recent similar analysis, in which Euro 83,500 were reported as the 1-year costs of patients having undergone LTx [35], but we question if this can be compared to our results, due to differences in the cost accounting methodologies. As the Dutch survival data which we used are highly crucial in our preliminary cost-effectiveness judgement of LTx for acute liver failure compared to LTx for chronic liver failure, we made a comparison of these data with survival data mentioned in the international literature (Table VI). This comparison supports the differences found on the basis of the Dutch survival data.

Notwithstanding this support, it should be borne in mind that our results can never be prescriptive for the question who should undergo transplantation and who not. The results are meant to provide better insight into the underlying costs of LTx in different patients and to show which items are the main drivers of these costs. Medication costs were highly dependent on the use of the anti-HBs immunoglobulin. Although it was administered in only 10% of the patient group, it determined 64% of the post-transplantation medication costs. This outlines the main drawback of our cost-effectiveness measure. For 25 patients per year, the annual average costs per patient of anti-HBs immunoglobuline were almost Euro 3,000. This means that the cost-effectiveness conclusion would already be reversed with an additional two chronic patients using anti-HBs immunoglobulin, if all other conditions remain the same. Besides, one could take the view that costs of patients who did not undergo transplantation should only be assigned to chronic patients, which would also make the results for these patients less favourable. Furthermore, it can be argued that 1-year survival is not the correct measure to reach a conclusion on cost-effectiveness of LTx in acute pa-

tients versus LTx in chronic patients. Beyond the observed survival rates of 83% in chronic patients and 62% in acute patients, it is known that survival without transplantation will be respectively about 50% [9] and 25% [38]. This means that in patients with acute liver failure, higher survival rates can be ascribed to the transplantation itself and, consequently, that LTx for acute liver failure is far more cost-effective when calculated according to our method. However, the opposite may be true if the number of life years gained by LTx are considered, as this number will be higher in chronic patients due, to the basic fact that more patients survive in this group. On the other hand, we observed that patients undergoing transplantation for acute liver failure were significantly younger than patients who underwent LTx for chronic liver failure. The life expectation per patient may therefore be longer in patients having survived LTx for acute liver failure.

Summarising, the 1-year costs of LTx for acute liver failure were almost 16% lower, then those of LTx for chronic liver failure. Our analysis aimed to provide a better understanding of the costs of LTx and the main drivers of these costs. Our 1-year cost-effectiveness measure favours LTx for chronic liver failure, although strong arguments can be made which are likely to reverse the result. To comprehensively assess cost-effectiveness, additional analyses have therefore to be performed, in which also quality of life analyses are included. Nevertheless, under the present budgetary restrictions our results are advantageous, for a centre aiming to gain more experience with LTx for acute liver failure as a way of improving patient survival, as LTx for acute liver failure is much less expensive than LTx for chronic liver failure.

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