ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

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ABSTRACT

BACKGROUND

A 6-month abstinence from alcohol is usually required before patients with severe alcoholic hepatitis are considered for liver transplantation. Patients whose hepatitis is not responding to medical therapy have a 6-month survival rate of approximately 30%. Since most alcoholic hepatitis deaths occur within 2 months, early liver transplantation is attractive but controversial.

METHODS

We selected patients from seven centers for early liver transplantation. The patients had no prior episodes of alcoholic hepatitis and had scores of 0.45 or higher according to the Lille model (which calculates scores ranging from 0 to 1, with a score ≥0.45 indicating nonresponse to medical therapy and an increased risk of death in the absence of transplantation) or rapid worsening of liver function despite medical therapy. Selected patients also had supportive family members, no severe coexisting conditions, and a commitment to alcohol abstinence. Survival was compared between patients who underwent early liver transplantation and matched patients who did not.

RESULTS

In all, 26 patients with severe alcoholic hepatitis at high risk of death (median Lille score, 0.88) were selected and placed on the list for a liver transplant within a median of 13 days after nonresponse to medical therapy. Fewer than 2% of patients admitted for an episode of severe alcoholic hepatitis were selected. The centers used 2.9% of available grafts for this indication. The cumulative 6-month survival rate (±SE) was higher among patients who received early transplantation than among those who did not (77±8% vs. 23±8%, $P<0.001$). This benefit of early transplantation was maintained through 2 years of follow-up (hazard ratio, 6.08; $P=0.004$). Three patients resumed drinking alcohol: one at 720 days, one at 740 days, and one at 1140 days after transplantation.

CONCLUSIONS

Early liver transplantation can improve survival in patients with a first episode of severe alcoholic hepatitis not responding to medical therapy. (Funded by Société Nationale Française de Gastroentérologie.)

Liver transplantation for alcoholic liver disease has a favorable outcome but remains controversial.[1,2] Reluctance to perform transplantation in patients with alcoholism is often based on the view that they are responsible for their illness and are likely to resume alcohol use after transplantation.[3] To select the most appropriate patients with severe forms of alcoholic liver disease for transplantation, most programs require a 6-month abstinence period before patients can be considered. Nevertheless, data regarding the 6-month rule as a predictor of long-term sobriety are controversial.[4] Despite the frequent use of the rule, the United Network for Organ Sharing and the French Consensus Conference[5] do not consider it to be a formal guideline.

Glucocorticoids have been recommended by recent U.S. guidelines to treat severe alcoholic hepatitis.[6] The Lille model enables early identification of patients unlikely to respond to medical treatment.[7,8] Strict application of the rule requiring 6 months of sobriety[9,10] may be disadvantageous to such patients, 70 to 80% of whom die within that period. Consequently, early liver transplantation should be evaluated in pilot studies restricted to carefully selected patients, as recommended by the latest French consensus.[5]

The aims of this study were to determine whether early liver transplantation improves the 6-month survival rate among patients whose severe alcoholic hepatitis is unresponsive to medical management, to evaluate the rate of alcohol relapse after transplantation in patients selected without applying the 6-month rule, and to evaluate the burden of early transplantation on the overall transplantation activity of participating centers.

METHODS

STUDY CONDUCT

Scientific committees from the Association Française d'Etude du Foie, the Association Française de Chirurgie Hépato-Biliaire et de Transplantation, and the Agence de Biomédecine (the French government agency in charge of graft allocation) approved the study. All selected patients provided written informed consent for transplantation surgery.

SELECTION OF THE STUDY PATIENTS

Seven transplant centers agreed to perform early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy. Alcoholic hepatitis was considered to be severe if the Maddrey's discriminant function was greater than 32, calculated as follows: $4.6 \times$ (patient's prothrombin time in seconds − matched control's prothrombin time in seconds) + patient's serum bilirubin level in milligrams per deciliter. A Maddrey's discriminant function of greater than 32 is the threshold for initiating glucocorticoid treatment.[6] Nonresponse to medical therapy was defined according to the Lille model as a score of 0.45 or more after 7 days of medical therapy or a continuous increase in the Model for End-Stage Liver Disease (MELD) score,[11] reflecting an early worsening of liver function. Medical therapy consisted of standard medical care for severe liver insufficiency and use of glucocorticoids (40 mg per day of prednisolone for at least 7 days). Nonresponse to medical therapy is associated with 6-month survival of approximately 30%.[7]

We selected patients with severe alcoholic hepatitis who were considered to be candidates for early transplantation, according to the following criteria: nonresponse to medical therapy (as defined above), severe alcoholic hepatitis as the first liver-decompensating event, presence of close supportive family members, absence of severe coexisting or psychiatric disorders, and agreement by patients (with support from family members) to adhere to lifelong total alcohol abstinence. The selection process consisted of several meetings between four medical team circles, the patient's family, and the patient. The team circles were as follows: first, the inner circle, closest to the patient, comprising nurses, one resident, and one fellow; second, a specialist in addiction; third, senior hepatologists; and fourth, the outermost circle, consisting of an anesthetist and surgeons. The four team circles had to reach complete consensus on selection.

This selection process was performed at all seven participating centers, which provided data on all early transplantations performed until September 1, 2010. The Lille and Brussels centers started the program in November 2005; the others began later. Two study patients did not receive glucocorticoids because their physicians considered the benefits to be negligible. Additional details about the selection process are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

ASSESSMENT OF ALCOHOL USE AFTER TRANSPLANTATION

After transplantation, alcohol use was assessed at short intervals during informal interviews of patients and their families performed according to the design of previous studies.[10,12,13] (See the Supplementary Appendix for additional details on assessment of alcohol use after transplantation.)

DATA COLLECTION

Development of biologic features of abnormal liver or kidney function was ascertained at least weekly from the first day of medical therapy until the patient was placed on the transplantation list. During the data collection period (i.e., the first day of medical therapy through 24 months after transplantation), we recorded data on all infections and subsequent treatment as well as any alcohol relapses, including those occurring more than 6 months after transplantation.

BURDEN OF EARLY LIVER TRANSPLANTATION

The total number of transplantations and the number of transplantations for alcoholic liver disease were reported annually by all centers, starting with the first early transplantation and until September 1, 2010. Only the Lille and Brussels centers had prospective databases of patients with biopsy-proven severe alcoholic hepatitis. These databases systematically recorded data for all patients with severe alcoholic liver disease meeting the criteria for nonresponse to medical

Table 1. Characteristics of the 26 Study Patients with Severe Alcoholic Hepatitis.*

Characteristic	Value
Male sex — no. (%)	15 (58)
Age — yr	
Median	47.4
Range	34.9–60.5
Glucocorticoid therapy — no. (%)	24 (92)
Duration of glucocorticoid therapy — days	
Median	12
Range	7–31
First day of medical therapy	
Prothrombin time — sec	
Median	23.2
Range	14.3–82.0
International normalized ratio	
Median	2.5
Range	1.3–5.8
Bilirubin — mg/dl	
Median	27.7
Range	10.0–61.3
Serum creatinine — mg/dl	
Median	0.82
Range	0.47–6.10
Albumin — g/liter	
Median	25
Range	14–33
Maddrey's discriminant function†	
Median	76
Range	36–165
MELD score‡	
Median	30.1
Range	22.0–47.3

Table 1. (Continued.)

Characteristic	Value
After 7 days of medical therapy	
Prothrombin time — sec	
Median	33.5
Range	11.0–56.0
International normalized ratio	
Median	2.2
Range	1.3–4.7
Bilirubin — mg/dl	
Median	28.4
Range	9.6–48.7
Serum creatinine — mg/dl	
Median	0.96
Range	0.48–4.95
Albumin — g/liter	
Median	27
Range	18–37
Lille score‡	
Median	0.880
Range	0.260–0.996
MELD score§	
Median	28.5
Range	23.0–52.4

* To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Maddrey's discriminant function is a measure of severity of alcoholic hepatitis and is calculated as follows: 4.6×(patient's prothrombin time in seconds−matched control's prothrombin time in seconds)+patient's serum bilirubin level in milligrams per deciliter. A score of more than 32 indicates severe alcoholic hepatitis and is the threshold for initiating glucocorticoid treatment.

‡ A Lille score of 0.45 or higher indicates nonresponse to medical therapy. The Lille score ranges from 0 to 1 and is calculated (www.lillemodel.com) with the use of the following formula: Exp (−R)/(1+Exp [−R]), where R=(3.19−0.101×age in years)+(0.147×albumin on day 0 in grams per liter)+([0.0165×change in bilirubin between day 0 and day 7 of medical therapy, in micromoles per liter]−[0.206×renal insufficiency {rated as 0 if absent and 1 if present}]−[0.0065×bilirubin level on day 0 in micromoles per liter]−[0.0096×prothrombin time in seconds]). In patients who received albumin infusions, the last available albumin value before infusion was used.

§ The Model for End-Stage Liver Disease (MELD) score is calculated (www.mayoclinic.org/meld/mayomodel7.html) as follows: (9.57×log creatinine in milligrams per deciliter)+(3.78×log bilirubin in milligrams per deciliter)+(11.20×log international normalized ratio)+6.43. Scores range from 6 to 42, with higher scores indicating a worse prognosis.

therapy and, for those not selected for early transplantation, the primary reason for exclusion.

CASE–CONTROL STUDY

Two patients whose disease was not responding to medical therapy — a case patient who underwent early transplantation and a control patient who did not — were matched with the use of two matching-selection processes. First, we nonrandomly selected the control patient who was the best fit for each case patient who underwent transplantation, according to age, sex, Maddrey's discriminant function, and Lille score (see the Supplementary Appendix).

Second, we randomly sampled control patients from a set of patients with severe alcoholic hepatitis who were listed in a combined prospective database of the Lille center. To avoid the risk of selecting the same control in the two matching procedures (nonrandom and random), we excluded all the matched controls who were already selected with the nonrandom matching procedure. The final combined database contained a total of 651 potential control patients. The random

selection was performed by means of the global optimal algorithm[14] (SAS software, version 9.2; SAS Institute) with the following preestablished ranges or values: age, ±10 years of the case patient's age; sex, same as the case patient; Maddrey's discriminant function, same category as the case patient's (<60, 60 to 90, or >90); and Lille score, ±0.15 of the case patient's score (see the Supplementary Appendix).

We also examined whether patients who underwent early liver transplantation owing to nonresponse to medical therapy had outcomes similar to patients whose disease had responded to medical therapy (i.e., those with a Lille score <0.45). To address this question, control patients with Lille scores less than 0.45 were matched to case patients on the basis of the global optimal algorithm, with terms for age, sex, and Maddrey's discriminant function (but not Lille score).

STATISTICAL ANALYSIS

Assuming 6-month survival rates of 70% among patients who underwent transplantation and 30% among the matched controls,[15,16] we calculated that at least 18 patients and 18 controls would have to be included for the study to have a statistical power of at least 80% to show a significant difference in the survival rate between the two groups. Variables were compared between the two groups with the use of chi-square tests and t-tests. The follow-up time was defined as the period from the first day of medical therapy to the last follow-up visit. In the case–control study, we estimated patients' rate of survival (expressed as a percentage ±SE) by means of the Kaplan–Meier method and compared survival between the two groups by using the log-rank test. The first day of medical therapy was defined as the first day of glucocorticoid administration or, for the two patients not treated with glucocorticoids, the first day of admission. The rate of 6-month survival — the primary end point — was measured from the first day of medical therapy to the date of death from any cause. In addition, we performed an analysis over an extended follow-up period of 2 years. Data for patients without events of interest were censored at the date of the last follow-up visit. A Cox proportional-hazards analysis, after adjustment for the MELD score and center (Lille vs. other centers), was also performed. All P values are two-tailed.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

Twenty-six patients with severe alcoholic hepatitis that had failed to respond to medical management underwent liver transplantation at the seven centers (Table 1). Alcoholic hepatitis was proved by biopsy specimens obtained by the transjugular route in 23 of the 26 case patients (88%) and confirmed in all case patients by means of histologic analysis of explants. The first transplantation was performed under this selection process on August 24, 2006, and the final one was conducted on June 16, 2010.

Nonresponse to medical therapy was defined as a Lille score of 0.45 or more in 25 patients and early worsening of liver function in 1 patient whose MELD score increased from 23 at day 7 to 36 at day 21, the day of listing (albeit whose Lille score was 0.26). A total of 24 of 26 patients were treated with glucocorticoids for 12 days (95% confidence interval [CI], 7 to 18). The remaining 2 patients did not receive glucocorticoids before referral to the transplantation unit. One had type 1 hepatorenal syndrome, and both had high Lille scores (0.88 and 0.66) within 7 days after hospitalization and before transfer to the transplantation center. For these 2 patients, the transplantation physicians believed that glucocorticoid therapy would have a negligible effect.[17]

MELD SCORES AND TRANSPLANTATION

The median MELD score at the time of listing as a candidate for transplantation was 34 (Table 2). The decision to list patients for transplantation was made soon after ascertainment of nonresponse to medical therapy (median, 13 days), and transplantation was performed soon after listing (median, 9 days afterward). Nonresponse to medical therapy was confirmed by the worsening of MELD scores until the time of listing. Substantial improvement before the time of listing (i.e., >10% decrease in the MELD score) was observed in three patients who underwent transplantation, after treatment with hepatic or renal support, which decreased bilirubin and creatinine levels.

SURVIVAL

Liver grafts were obtained from cadaveric donors (see the Supplementary Appendix). Patients who underwent transplantation and controls were well-matched (Table 3). The 6-month survival rate

was significantly higher among patients undergoing transplantation (77±8%) than among matched controls (23±8%, P<0.001) (Fig. 1). The benefit of performing early transplantation was supported by the fact that 90% of deaths (18 of 20) among control patients occurred within 2 months after identification of nonresponse to medical therapy (Fig. 1).

After transplantation, five of six deaths were related to infection occurring within 2 weeks after surgery; the infection was invasive aspergillus infection in four cases. Cerebral aspergillosis developed in one patient who had undergone transplantation and survived; it was rapidly treated with voriconazole. The patients undergoing transplantation who died did not differ significantly from those who remained alive, although the duration of glucocorticoid therapy was longer (see the Supplementary Appendix).

Additional analysis with extension of follow-up to 2 years showed that transplantation remained associated with survival in univariate analyses (71±9% vs. 23±8%, P<0.001) (Fig. 1) and multivariate analyses (hazard ratio, 6.08; 95% CI, 1.77 to 20.88; P=0.004) adjusted for the center (Lille vs. other centers) and the MELD score.

Use of the global optimal algorithm resulted in the random selection of 69 additional matched controls who were nonresponders to medical therapy and 92 additional matched controls who were responders. The 69 randomly selected matched controls whose disease was nonresponsive to medical therapy were not significantly different from the 26 patients who underwent transplantation in terms of male sex (59.4%, P=0.90), median age (control group, 51.8 years; 95% CI, 47.0 to 53.8; P=0.19 for comparison with case patients), median Maddrey's discriminant function (control group, 70.8; 95% CI, 64.2 to 82.3; P=0.79), and Lille score (control group, 0.87; 95% CI, 0.80 to 0.93; P=0.66). The 92 randomly selected matched controls whose disease did respond to medical therapy were not significantly different from the 26 case patients in terms of male sex (57.7%, P=0.60), median age (control group, 46.2 years; 95% CI, 45.0 to 48.1; P=0.37), and median Maddrey's discriminant function (control group, 68.2; 95% CI, 65.4 to 76.0; P=0.33), but as expected, the responder control group had lower Lille scores (0.18; 95% CI, 0.10 to 0.21; P<0.001) than the case-patient group. The 6-month survival rate was higher among the 26 case patients who underwent transplantation than among the nonresponder controls (77±8% vs. 30±6%, P<0.001) but not significantly different than the rate among the responder controls (77±8% vs. 85±4%, P=0.33) (Fig. 2).

Table 2. Clinical and Biologic Events between Study Enrollment and Listing for Liver Transplantation in the 26 Study Patients with Severe Alcoholic Hepatitis.

Event	Value
Bacterial infection — no. (%)*	18 (69)
Ascites	6 (23)
Pulmonary	5 (19)
Urinary	4 (15)
Bacteremia	5 (19)
Other	2 (8)
Gram-negative bacteria	9 (35)
Gram-positive cocci	6 (23)
Pneumocystis carinii	2 (8)
Fungal infection	3 (12)
Spontaneous bacterial peritonitis without identifiable bacteria	2 (8)
Hepatorenal syndrome — no. (%)	15 (58)
Renal support or molecular adsorbent recirculating system — no. (%)	10 (38)
Gastrointestinal bleeding — no. (%)	4 (15)
Mechanical ventilation — no. (%)	4 (15)
Time from end of glucocorticoid treatment to listing — days	
Median (95% CI)	13 (6 to 17)
Range	1 to 46
MELD at time of listing	
Median (95% CI)	34 (29 to 37)
Range	25 to 41
Difference in MELD between nonresponse and listing†	
Median (95% CI)	–1.9 (–6.0 to 0.0)
Range	–14.2 to 14.4
Time from listing to liver transplantation — days	
Median (95% CI)	9 (3 to 11)
Range	1 to 37

* Infection developed at multiple sites in four patients.
† Nonresponse to medical therapy was determined after 7 days of medical therapy. All improvements were related to the use of a molecular adsorbent recirculating system or renal-replacement therapy.

BURDEN OF EARLY LIVER TRANSPLANTATION

During the study period, 891 transplantations were performed at the seven centers; 315 of these transplantations were for alcoholic liver disease. A total of 26 of all 891 procedures (2.9%) and 26 of the 315 procedures for alcoholic liver disease (8.3%) were early transplantations.

Table 3. Results of Case–Control Comparisons of the 26 Study Patients and 26 Matched Controls.*

Characteristic	Patients Who Underwent Transplantation	Matched Controls	P Value
Living with a partner — no. (%)	17 (65)	13 (50)	0.19
Employed — no. (%)	17 (65)	16 (62)	0.92
Male sex — no. (%)	15 (58)	15 (58)	1.00
Age — yr			0.34
Median (range)	47.4 (34.9–60.5)	50.6 (34.5–60.6)	
95% CI	42.6–52.4	46.5–52.6	
First day of medical therapy			
Maddrey's discriminant function			0.56
Median (range)	76.0 (35.6–165.0)	80.6 (48.4–202.0)	
95% CI	61.2–91.0	66.4–97.5	
Lille score			0.28
Median (range)	0.880 (0.260–0.996)	0.827 (0.250–0.999)	
95% CI	0.760–0.950	0.690–0.874	
MELD score			0.27
Median (range)	30.1 (22.0–47.3)	29.1 (19.1–40.0)	
95% CI	27.1–33.4	25.6–32.4	
Prothrombin time — sec			0.63
Median (range)	23.2 (14.3–82.0)	24.1 (16.7–51.5)	
95% CI	18.9–27.8	20.7–26.6	
Bilirubin — mg/dl			0.61
Median (range)	27.7 (10.0–61.3)	26.2 (4.7–65.0)	
95% CI	19.1–31.8	17.4–34.7	
Serum creatinine — mg/dl			0.11
Median (range)	0.8 (0.5–6.1)	1.1 (0.6–3.8)	
95% CI	0.6–1.1	0.8–1.4	
Albumin — g/liter			0.42
Median (range)	25 (14–33)	24 (11–36)	
95% CI	23–29	21–26	
After 7 days of medical therapy			
MELD score			0.47
Median (range)	28.5 (23.0–52.4)	29.4 (19.4–60.2)	
95% CI	26.2–33.7	25.6–31.8	
Prothrombin time — sec			0.63
Median (range)	22.2 (14.2–59.0)	23.5 (14.7–70.0)	
95% CI	20.7–24.5	20.3–26.3	
Bilirubin — mg/dl			0.58
Median (range)	28.4 (9.6–48.7)	27.7 (4.3–66.8)	
95% CI	24.7–34.1	20.1–34.6	
Creatinine — mg/dl			0.26
Median (range)	1.0 (0.5–5.0)	1.2 (0.6–5.2)	
95% CI	0.6–1.2	0.9–1.4	
Albumin — g/liter			0.52
Median (range)	27 (18–37)	27 (21–51)	
95% CI	24–30	24–30	

* To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert values for bilirubin to micromoles per liter, multiply by 17.1.

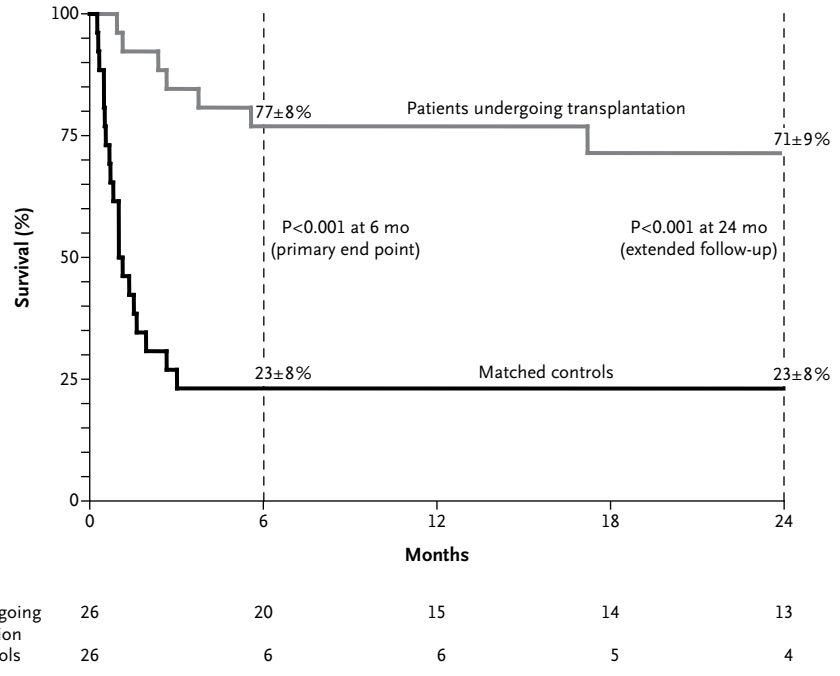


Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

In all, 233 patients were admitted for severe alcoholic hepatitis at the Brussels center (52 patients) and the Lille center (181 patients). A total of 18 of the 233 underwent transplantation (see Table 1 in the Supplementary Appendix), 14 of whom had been referred by community hospitals. The remaining 4 were directly selected by the Brussels and Lille centers through their own recruitment of patients with severe alcoholic hepatitis (representing 1.8% of the 219 patients who had not undergone transplantation or referral by community hospitals). The reason for exclusion from early transplantation was a predisposition to addiction or unfavorable social or familial profiles in approximately 90% of nonresponders with severe alcoholic liver disease.

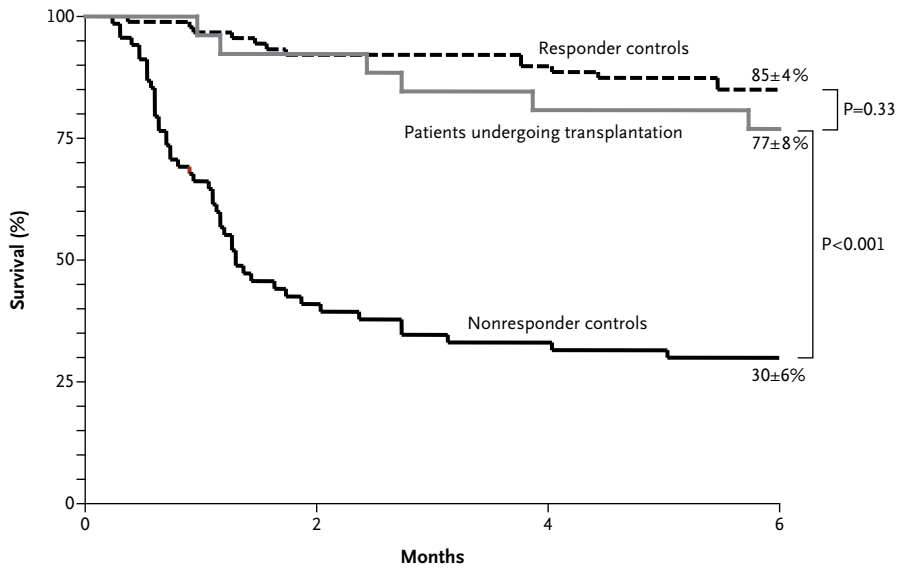
FOLLOW-UP AND ASSESSMENT OF ALCOHOL RELAPSE

In case patients who were alive at 6 months, liver tests and creatinine levels returned to normal ranges within the first month after transplantation. There was no significant difference between the 1-month and 6-month values of the aminotransferases, γ-glutamyltransferase, creatinine, or international normalized ratio (see the Supplementary Appendix), although the median total bilirubin level declined from 1.9 mg per deciliter (32.5 μmol per liter) (95% CI, 1.5 to 3.0 mg per deciliter [25.6 to 51.3 μmol per liter]) at 1 month to 0.7 mg per deciliter (12.0 μmol per liter) (95% CI, 0.6 to 1.1 mg per deciliter [10.3 to 18.8 μmol per liter]) at 6 months (P<0.001).

After transplantation, patients were followed at short intervals, with a median of 11 visits (95% CI, 9 to 13) during the 6-month period. Since that time, follow-up is ongoing, with a median of 11 visits (95% CI, 5 to 14) at a median interval of 1.8 months (95% CI, 0.7 to 2.3). No alcoholic relapse was observed within the initial 6-month follow-up period. Three of 26 patients later resumed drinking alcohol, one at 720 days, one at 740 days, and one at 1140 days after transplantation. Despite counseling by an addiction specialist, 2 patients remained daily consumers (30 g per day and >50 g per day), whereas 1 drank occasionally (approximately 10 g per week). None of them has had graft dysfunction.

DISCUSSION

The high risk of early death[7,17] in patients with severe alcoholic hepatitis not responding to medical therapy[11,18,19] makes it necessary to consider all available treatment options, including transplantation, in targeted patients.[20] Choosing the



No. at Risk				
Responder controls	92	77	75	71
Patients undergoing transplantation	26	21	21	20
Nonresponder controls	69	21	21	19

Figure 2. Kaplan–Meier Estimates of Survival among the 26 Study Patients and Randomly Selected Matched Controls.

appropriate moment for transplantation is crucial, to avoid adverse effects of intervening too soon or too late.[21] This prospective multicenter study showed that early transplantation clearly improves the probability of 6-month survival among patients in whom medical therapy failed. We selected control patients by using two different processes of matching so as to reduce investigator bias and limit period and cohort effects.

Team members requested stringent selection for at least two reasons. First, donor grafts remain in short supply. Second, in the allocation system based on MELD scores, patients with severe alcoholic hepatitis who are not having a response to medical therapy are likely to rank at the top of the transplant waiting list. Therefore, team members believed that patients who were unaware of their underlying liver disease constituted the most urgent problem. However, the exclusion of patients with previous episodes of liver decompensation raises an ethical question, since there is no agreement about the rationale for excluding alcoholic patients from transplantation.[22]

Studies evaluating the usefulness of fungal prophylaxis before transplantation, duration of glucocorticoid use before and after transplantation, and the tailoring of immunosuppressive regimens are warranted in light of the deaths due to aspergillosis.

Our findings challenge both the notion of a prescribed abstinence period as the only alcoholism-related criterion for transplant eligibility[23] and the opinion of experts that alcoholic hepatitis is a contraindication for transplantation.[24] However, the stringency of our selection process resulted in our selecting a very small number of patients with alcoholic hepatitis for early transplantation. Although numerous studies have lent support to the validity of a sobriety period, they also have observed that the enforcement of this period alone delays listing for transplantation a considerable number of candidates with a low probability of relapse.[10,25-30] Indeed, the duration of abstinence before transplantation is a poor predictor of relapse of alcoholism.[31] Organization of the medical staff into four team circles should have ensured a balanced selection process. No relapse of alcoholism was observed during the 6 months following transplantation, although three patients had a relapse later. This low rate of relapse was probably related to our stringent selection of candidates for transplantation; for

instance, physicians from Lille and Brussels selected fewer than 2% of the patients with severe alcoholic hepatitis recruited at their centers.

Regarding organ shortage,[32] early liver transplantation accounted for only 2.9% of grafts used during the study period. Nevertheless, modifications in guidelines for liver transplantation in patients with alcoholism may conflict with public preferences for liver-transplant allotment[33,34] and may decrease willingness to donate.[3] However, this has not occurred in response to transplantation being offered to patients with fulminant hepatic failure due to voluntary acetaminophen poisoning, nor to intravenous-drug users with acute hepatitis B virus infection. The limited supply of donor organs frequently biases what should be equal access to potential medical benefits for all patients.[35] Development of an international database collecting information on survival and addiction is warranted to provide more facts and less conjecture in future discussions of the role of early transplantation in the treatment of severe alcoholic hepatitis.[36]

Although our data are encouraging, the study did have limitations. The design did not allow for rigorous assessment of long-term outcomes. Matched controls may not have been comparable to patients in terms of support of family members, intentions of patients to remain alcohol-free, or availability of counseling in the event of a return to drinking. Future studies elucidating long-term outcomes will require a control group of patients with alcoholism undergoing transplantation after abstaining from alcohol for a 6-month period who are matched to patients on the basis of social and familial characteristics. Previous studies of patients with alcoholism who underwent transplantation suggest that the rate of relapse over the long term may be approximately 25 to 35%.[10,12,13] Finally, reproducibility of the selection process needs to be attempted. In summary, early liver transplantation may be an appropriate rescue option for selected patients whose first episode of severe alcoholic hepatitis is not responsive to medical therapy, after careful assessment of their addiction profile. Our encouraging results must be confirmed by other groups.

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