Early liver transplantation for severe alcohol-related hepatitis not responding to medical treatment: a prospective controlled study

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Summary

Background Early liver transplantation for severe alcohol-related hepatitis is an emerging treatment option. We aimed to assess the risk of alcohol relapse 2 years after early liver transplantation for alcohol-related hepatitis compared with liver transplantation for alcohol-related cirrhosis after at least 6 months of abstinence.

Methods We conducted a multicentre, non-randomised, non-inferiority, controlled study in 19 French and Belgian hospitals. All participants were aged 18 years or older. There were three groups of patients recruited prospectively: patients with severe alcohol-related hepatitis who did not respond to medical treatment and were eligible for early liver transplantation according to a new selection scoring system based on social and addiction items that can be quantified in points (early transplantation group); patients with alcohol-related cirrhosis listed for liver transplantation after at least 6 months of abstinence (standard transplantation group); patients with severe alcohol-related hepatitis not responding to medical treatment not eligible for early liver transplantation according to the selection score (not eligible for early transplantation group), this group did not enter any further liver transplantation processes. We also defined a historical control group of patients with severe alcohol-related hepatitis unresponsive to medical therapy and non-transplanted. The primary outcome was the non-inferiority of 2-year rate of alcohol relapse after transplantation in the early transplantation group compared with the standard transplantation group using the alcohol timeline follow back (TLFB) method and a prespecified non-inferiority margin of 10%. Secondary outcomes were the pattern of alcohol relapse, 2-year survival rate post-transplant in the early transplantation group compared with the standard transplantation group, and 2-year overall survival in the early transplantation group compared with patients in the not eligible for early transplantation group and historical controls. This trial is registered with ClinicalTrials.gov, NCT01756794.

Findings Between Dec 5, 2012, and June 30, 2016, we included 149 patients with severe alcohol-related hepatitis: 102 in the early transplantation group and 47 in the not eligible for early transplantation group. 129 patients were included in the standard transplantation group. 68 patients in the early transplantation group and 93 patients in the standard transplantation group received a liver transplant. 23 (34%) patients relapsed in the early transplantation group, and 23 (25%) patients relapsed in the standard transplantation group; therefore, the non-inferiority of early transplantation versus standard transplantation was not demonstrated (absolute difference 9·1% [95% CI –∞ to 21·1]; p=0·45). The 2-year rate of high alcohol intake was greater in the early transplantation group than the standard transplantation group (absolute difference 16·7% [95% CI 5·8–27·6]) The time spent drinking alcohol was not different between the two groups (standardised difference 0·24 [95% CI –0·07 to 0·55]), but the time spent drinking a large quantity of alcohol was higher in the early transplantation group than the standard transplantation group (standardised difference 0·50 [95% CI 0·17–0·82]). 2-year post-transplant survival was similar between the early transplantation group and the standard transplantation group (hazard ratio [HR] 0·87 [95% CI 0·33–2·26]); 2-year overall survival was higher in the early transplantation group than the not eligible for early transplantation group and historical controls (HR 0·27 [95% CI 0·16–0·47] and 0·21 [0·13–0·32]).

Interpretation We cannot conclude non-inferiority in terms of rate of alcohol relapse post-transplant between early liver transplantation and standard transplantation. High alcohol intake is more frequent after early liver transplantation. This prospective controlled study confirms the important survival benefit related to early liver transplantation for severe alcohol-related hepatitis; and this study provides objective data on survival and alcohol relapse to tailor the management of patients with severe alcohol-related hepatitis.

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Research in context

Evidence before this study

The treatment of patients with alcohol-related liver disease has changed markedly over time, which is a result of more personalised management. Severe alcohol-related hepatitis is a life-threatening condition, and corticosteroids for 1 month are the only approved medical treatment; this treatment unfortunately leads to non-response in around 30–40% of patients who have a high risk of death. No pharmacological option has been proven efficient, and these patients are at a therapeutic end. In a collaborative French and Belgian pilot study published in 2011, early liver transplantation was suggested as a rescue option for patients with severe alcohol-related hepatitis not responding to medical treatment. Additional evidence from the USA seems to confirm the benefit of early liver transplantation in carefully selected patients. However, these data are only based on cohort studies, and no controlled trial data were available before the present work. We searched PubMed with no language limitations using the terms "alcoholic hepatitis", "transplantation", "alcoholic cirrhosis", "6-month rule", "drug", and "therapy". We also searched the ClinicalTrials.gov database for clinical trials in alcohol-related hepatitis. The search was censored on Jan 31, 2010, when the trial protocol was completed. We compared the rate of alcohol relapse in patients with severe alcohol-related hepatitis not responding to medical treatment selected for early liver transplantation (early transplantation group), and patients with alcohol-related cirrhosis with at least 6 months of abstinence (standard transplantation group). Patients in the early transplantation group were not abstinent when alcohol-related hepatitis occurred.

Added value of this study

To our knowledge, this is the first prospective controlled trial in the field that systematically recorded alcohol relapse after transplantation using the validated alcohol timeline follow back (TLFB) tool. Selection of patients for early liver transplantation using a new scoring algorithm was repeatable between centres. Compared with standard transplantation for alcohol-related cirrhosis with a period of at least 6 months abstinence, we cannot conclude non-inferiority in terms of alcohol relapse after early liver transplantation. High levels of alcohol consumption were more frequently seen in patients who underwent early liver transplantation for alcohol-related hepatitis than in patients with alcohol-related cirrhosis who received standard transplantation (ie, after 6 months of abstinence). This study also adds important data on alcohol consumption through the use of the TLFB method. At 2 years, no difference was observed in survival between patients who received a liver transplant in the early transplantation group and patients who received a liver transplant in the standard transplantation group. Compared with the two separate non-transplanted control groups, early liver transplantation markedly improves survival of patients with severe alcohol-related hepatitis.

Implications of all the available evidence

This study provides objective data on the rate of alcohol relapse after transplantation and survival rates, which could alter the management of patients with severe alcohol-related hepatitis. An integrative approach to test specific strategies to reduce the risk of alcohol relapse should be assessed in these patients.

Introduction

Patients with severe alcohol-related hepatitis who do not respond to medical management and have around 80% risk of 6-month mortality can now be identified with prognostic scores such as the Lille model.[1] Because these patients are at a therapeutic end and there is improved prediction of mortality, the French consensus on liver transplantation[2] has recommended investigating early access to liver transplantation without a period of at least 6 months of abstinence. A pilot study[3] reported a significant benefit to survival following early liver transplantation in highly selected patients, which has been confirmed by several other studies.[4–6] The risk of alcohol relapse was estimated in 2018 to be around 30% in patients who survive to home discharge.[5] Unfortunately, most studies have been retrospective and not controlled. Based on the encouraging results of the pilot studies, many European and American centres have modified their policies for early liver transplantation. In France, the early liver transplantation programme began in 2005, and the percentage of centres performing this procedure increased from 35% in 2011 to 88% in 2018.[7] In the USA, this strategy was implemented after 2011, and the percentage of centres performing early liver transplantation increased from 27% in 2015, to 51% in 2018.[8,9] However, heterogeneity persists among countries, Italy endorses early liver transplantation;[10] Canada continues to list alcohol-related hepatitis as a contraindication to liver transplantation;[11] and Germany requests the approval of a committee of specialists for each early liver transplantation.[12] Reluctance persists because some experts fear that in the context of graft shortages, early liver transplantation could reduce public willingness to donate organs.[13,14] This reluctance can be explained in part by the absence of direct comparisons of alcohol relapse between patients who undergo early liver transplantation for severe alcohol-related hepatitis and patients transplanted for alcohol-related cirrhosis with a minimum period of abstinence.

In the present study, we compared patients with severe alcohol-related hepatitis who received early liver transplantation with patients who received a liver transplant for alcohol-related cirrhosis after 6 months or more of alcohol abstinence. On the basis of factors associated with alcohol relapse, such as younger age and a lack of strong family support,[15,16] and experience from

the pilot study,[3] we developed a new algorithm to select candidates for early liver transplantation. The aims of the study were to assess the risk of alcohol relapse 2 years after early liver transplantation compared with standard liver transplantation after 6-month abstinence, to quantify the benefit of early liver transplantation on 2-year survival compared with that of standard liver transplantation, to determine the profile of alcohol consumption after liver transplantation in these two groups, and to compare 2-year overall survival in the early transplantation group with that of patients in the not eligible for early transplantation group and non-transplanted historical controls.

Methods

Study design and participants

This prospective, non-randomised, non-inferiority controlled trial, termed QuickTrans, was performed in 19 French and Belgian hospitals. Patients were selected for early liver transplantation using a specific score that was constructed by the Lille team on the basis of previously proposed social and addiction criteria.[3] The score was constructed by the senior members of the team who converted the relevance of each criterion into points (appendix pp 2–7). To evaluate the reproducibility of the algorithm, we recorded the consensus meeting of the last seven patients in the study with severe alcohol-related hepatitis who were evaluated for early liver transplantation in the transplantation centre in Lille, France. After the end of the recruitment period, these videos were sent to the participating centre in Besançon, France, and the algorithm was scored by an independent consensus team that was not aware of the scores given by the Lille team.

There were three groups of patients recruited prospectively: patients with severe alcohol-related hepatitis who did not respond to medical treatment and were listed for early liver transplantation if the score from the selection algorithm constructed for the study was 220 points or higher (early transplantation group); patients with alcohol-related cirrhosis listed for liver transplantation after at least 6 months of abstinence (standard transplantation group); and patients with severe alcohol-related hepatitis not responding to medical treatment not listed for early liver transplantation because the score from the algorithm was less than 220 (not eligible for early transplantation group), this group did not enter any further liver transplantation processes. For the case-control study, patients in the early transplantation group were matched to patients with biopsy-proven severe alcohol-related hepatitis unresponsive to medical therapy included in the prospective Lille liver database (428 patients from 2002 to 2019 [historical control group]). These non-transplanted controls were randomly matched, using a 1:1 ratio with cases and the global optimal matching algorithm based on the following predefined criteria: age absolute difference (|age of cases minus age of controls| ≤10 years), Maddrey function score at initiation of medical treatment (treated as a three-level categorical variable: <60, 60–90, >90), and Lille model score absolute difference (|Lille model score of cases minus Lille model score of controls| ≥0·15).

Informed written consent was obtained from patients or their relatives (in case of severe encephalopathy) in all participants. The study was approved by the Nord Ouest IV institutional review board and ethics committee, and complied with Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws.

To be included in the study, all patients needed to be aged 18 years or older. Patients with alcohol-related hepatitis assigned to the early transplantation group and the not eligible for early transplantation group were included in the study if they fulfilled the following criteria: high alcohol intake, clinical diagnosis of alcohol-related hepatitis, hospitalised for less than 1 month (biopsy-proven in most cases via transjugular route for all patients according to routine French and Belgian practices, except in case of technical failure), Maddrey score of 32 or higher at admission, and poor response to medical management[1] (Lille model score ≥0·45) or early worsening of liver function despite an initial good therapeutic response (Lille model score <0·45).

See Online for appendix

Patients were included in the standard transplantation group if they were listed for liver transplantation for alcohol-related cirrhosis with at least 6 months of abstinence. Exclusion criteria in all groups were the presence of HBsAg, hepatitis C virus, HIV antibodies, pregnancy, breastfeeding, evolving neoplasia likely to threaten 1-year outcome, and uncontrolled bacterial, fungal, parasitic, or viral infection.

Data collection

After inclusion, patients in the early transplantation group and standard transplantation group were followed up regularly until liver transplantation, and patients who received a liver transplant were included in the primary analysis, using the date of liver transplantation as the date of inclusion, and followed up for 2 years after transplantation. Patients from the not eligible for early transplantation group were followed up for 2 years.

Patients were followed up every week for the first month after liver transplantation, then every month until 6 months, and at 9, 12, 18, and 24 months thereafter. All patients were advised to abstain from alcohol after liver transplantation. Any alcohol consumption was considered inappropriate and was recorded using the alcohol timeline follow back (TLFB),[17] for up to 2 years. The TLFB is a validated tool to assess efficacy outcomes in alcohol use disorder pharmacotherapy trials. Alcohol relapse was defined as at least 1 day with any alcohol consumption during the 2-year follow-up period. We defined high alcohol consumption as 30 g/day or more in women and 40 g/day or more in men. In addition, an addiction

specialist or hepatologist performed clinical interviews of patients and family members on the patient's alcohol use. Addiction management was the same in all study groups, and it was performed according to the local practice at the centre, not prespecified by the study design.

Outcomes

The primary outcome was the 2-year rate of alcohol relapse after transplantation in the early transplantation group compared with the standard transplantation group using the TLFB method,[17–19] with a prespecified non-inferiority margin of 10%. Secondary outcomes were the pattern of alcohol relapse and 2-year survival after transplantation in the early transplantation group compared with the standard transplantation group, and 2-year overall survival in the early transplantation group (ie, transplanted or not) compared with patients in the not eligible for early transplantation group and historical controls (ie, not transplanted). Pattern of relapse was analysed by the percentage of time (days) spent drinking any alcohol after liver transplantation, the frequency of high alcohol intake within the 2 years after liver transplantation, and the percentage of follow-up time spent drinking a high quantity of alcohol after liver transplantation.

This study evaluated transplantation, a routine practice in transplant medicine (Belgium and France). Consequently, events other than alcohol relapse, graft loss, and death after liver transplantation were not considered.

Statistical analysis

We did a non-inferiority analysis of the primary outcome (2-year rate of alcohol relapse) in the early transplantation

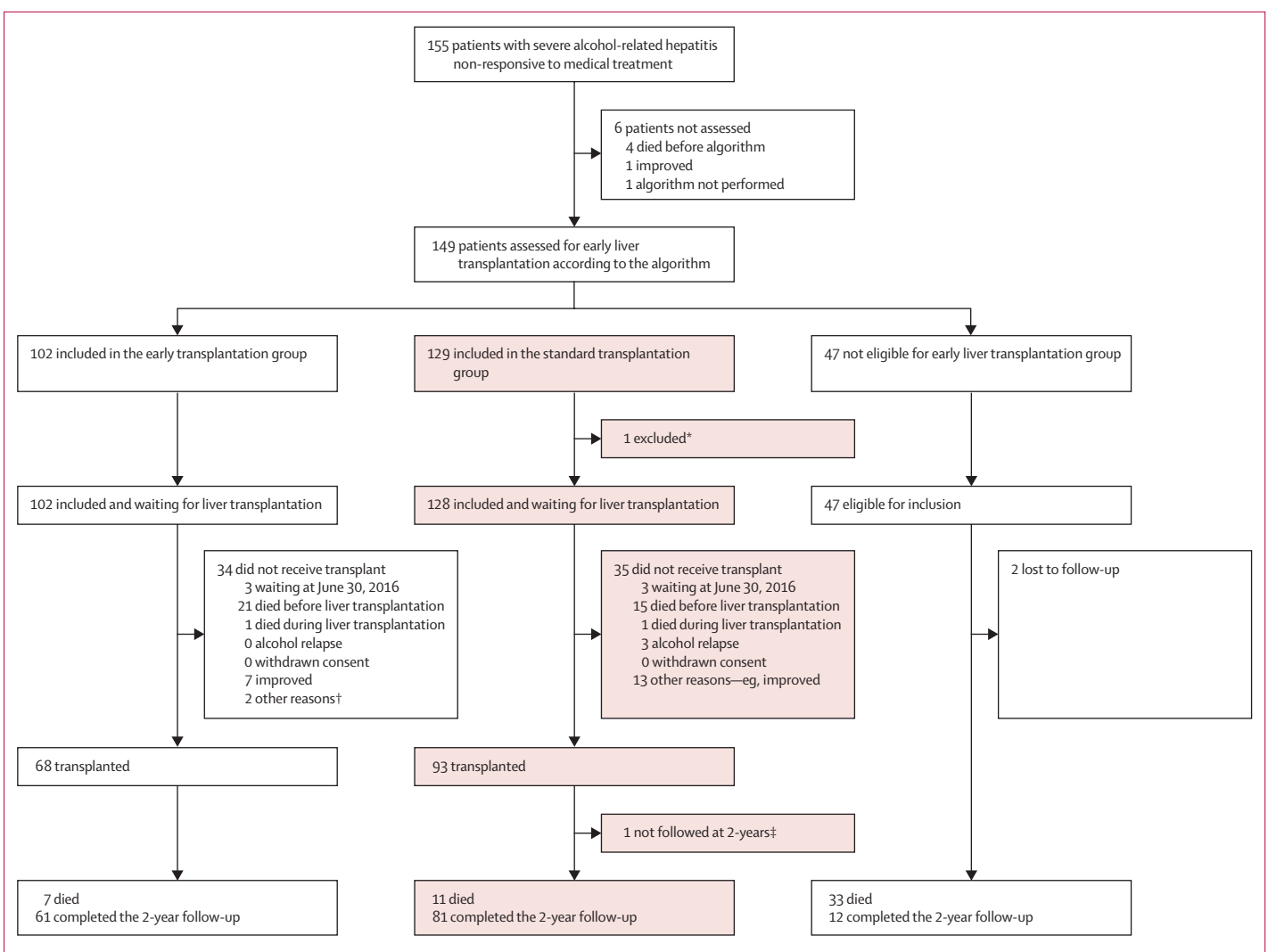

Figure 1: **Flowchart of the study**

*This patient was not listed because of a respiratory contraindication to liver transplantation. †One patient had a contraindication for liver transplantation and one patient's family refused liver transplantation. ‡This patient decided to stop the study follow-up without withdrawing consent to participate.

group compared with the standard transplantation group using the TLFB method,[17–19] with a prespecified non-inferiority margin of 10%. We calculated that 49 transplanted patients with an accelerated procedure (early transplantation group, experimental) and 74 transplanted patients with a standard procedure (standard transplantation group, control) were needed for a statistical power of 80%, to demonstrate that the accelerated procedure was not inferior to the standard procedure for 2-year alcohol relapse with a one-sided test at 0·05 significance level. The sample size was calculated on the basis of an unbalanced sample ratio of 1·5, assuming a 2-year rate of alcohol relapse of 10% in the early transplantation group and 15% in the standard transplantation group, and a non-inferiority margin of 10%. Considering an anticipated 2-year mortality after transplantation of 20% in the early transplantation group and 10% in the standard transplantation group, we planned to stop recruitment when at least 62 patients in the early transplantation group and 83 patients in standard transplantation group were transplanted.

The primary efficacy non-inferiority analysis was performed in all transplanted patients in the early transplantation group and all transplanted patients in the standard transplantation group, and follow-up time was defined as the period from the date of transplantation to 2 years after transplantation. We estimated the upper bound 95% CI of the absolute difference of the 2-year rate of alcohol relapse between the early transplantation group and standard transplantation group. This rate of alcohol relapse was calculated as the proportion of patients with alcohol relapse out of the transplanted patients. Non-inferiority was confirmed if the upper bound 95% CI was less than 10%. No correction for multiple comparisons was applied for other analyses and the results are reported only using effect size estimates with their 95% CI. The differences between the transplanted patients in the early transplantation group and the transplanted patients in the standard transplantation group are expressed in absolute and relative risks for the 2-year high alcohol intake rate, standardised difference (calculated in rank-transformed data) for the percentage of follow-up time spent drinking any alcohol and high alcohol intake, and hazard ratio ([HR] calculated using Cox's proportional hazard regression model) for 2-year overall survival (using the Kaplan-Meier method). Patients lost to follow-up were censored at the last follow-up. Sensitivity analyses for the primary outcome and 2-year high alcohol intake were performed using competing risk survival analysis, treating death as competing events by reporting the absolute difference in the 2-year cumulative incidence (estimated using Kalbfleisch and Prentice method) and the subhazard ratio (calculated using Fine and Gray regression model) as effect sizes.

Pre-specified secondary analyses of patients with severe alcohol-related hepatitis from the early transplantation group, not eligible for early transplantation group, and the historical control group were performed, considering the date of non-response to medical treatment as the first day of survival follow-up. The differences in 2-year overall survival in the early transplantation group versus the not eligible for early transplantation group and the historical control group were expressed as HRs calculated with the Cox proportional-hazards regression model, with a sandwich variance estimator to compare the early transplantation group with the historical control group to account for the matched design.

Analyses were performed with SAS (version 9.4), further details on statistical analysis are described in the statistical analysis plan (appendix pp 13–28). The study was registered under European policy number, EudraCT 2006–006944–78 and with ClinicalTrials.gov, NCT01756794.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 5, 2012, and June 30, 2016, 155 patients with severe alcohol-related hepatitis who did not respond to medical treatment and had a median Lille model score

	Early transplantation group (n=68)	Standard transplantation group (n=93)
Age, years	54 (46–59)	56 (52–60)
Gender		
Male	46 (68%)	68 (73%)
Female	22 (32%)	25 (27%)
Alcohol consumption, units per day	12 (8–20)	0
Ascites, any grade	52/66 (79%)	62/92 (67%)
Encephalopathy	12/66 (18%)	11/92 (12%)
Patient treated with corticosteroids	65 (96%)	0
Prothrombin time, s	25·4 (20·7–30·6)	22·9 (19·7–27·2)
INR*	2·3 (1·9–2·9)	2·0 (1·8–2·4)
Leukocyte count, cells per µL	16 405 (12 850–20 955)	5500 (4110–7900)
Bilirubin, mg/dL	24·2 (17·9–31·2)	6·1 (3·8–9·1)
Serum creatinine, mg/dL†	1·1 (0·7–1·8)	0·8 (0·6–1·2)
Albumin, g/L‡	28 (24–33)	31 (27–35)
AST, IU/L§	94 (76–118)	51 (40–73)
MELD score	31 (26–35)	22 (19–26)

Data are median (IQR), n (%), or n/N (%). INR=International Normalised Ratio. AST=aspartate aminotransferase. MELD=Model for End-stage Liver Disease.
*One missing value for INR (n=1 in standard transplantation group).
†Three missing values for creatinine (n=1 in the standard transplantation group).
‡27 missing values for albumin (n=13 in the standard transplantation group).
§Four missing values for AST (n=2 in the standard transplant group).

Table 1: **Patient characteristics at liver transplantation in the early transplantation group and the standard transplantation group enrolled in the QuickTrans study**

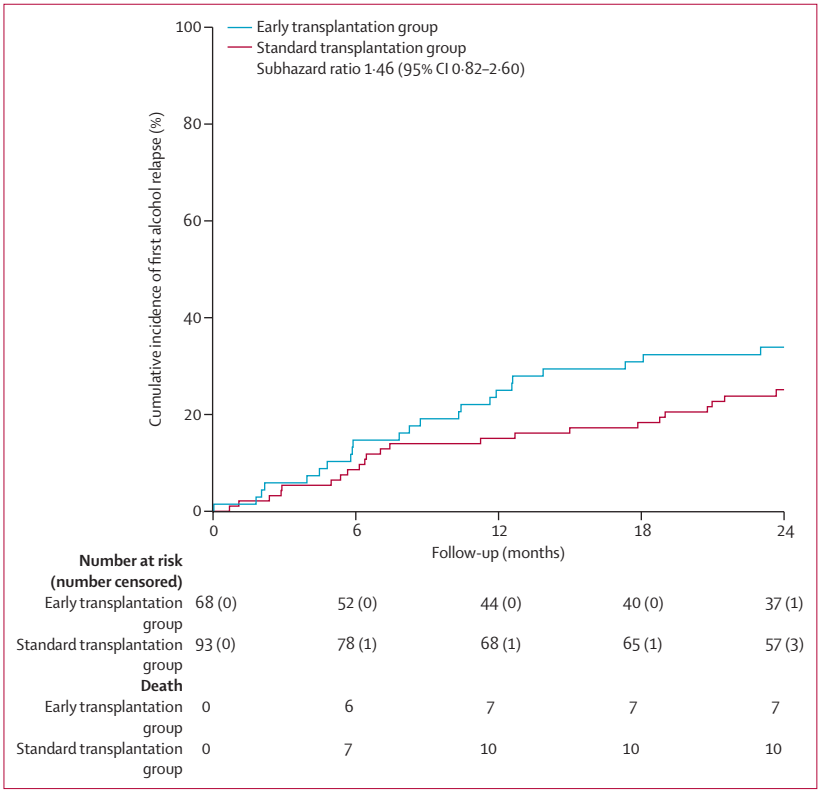

Figure 2: **2-year cumulative incidence of first alcohol relapse after liver transplantation in the early transplantation group and standard transplantation group enrolled in the QuickTrans study**

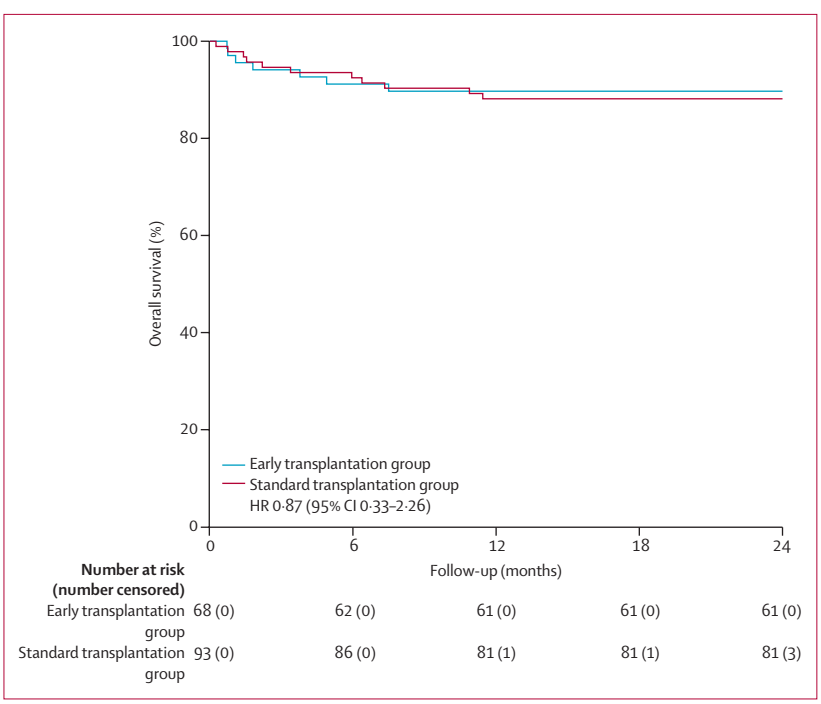

Figure 3: **2-year overall survival after liver transplantation in the early liver transplantation group compared with the standard transplantation group in the QuickTrans study**

of 0·84 were eligible for this study. Six patients were not assessed; thus, 149 patients were included (figure 1). After evaluation using the constructed algorithm, 47 patients were not selected for early liver transplantation and entered the not eligible for early transplantation group with a median score of 188 points (IQR 158–207, range 56–218). The remaining 102 patients entered the early transplantation group with a median score of 234 points (IQR 228–239, range 202–246). We observed one minor deviation in the protocol: one patient with a score of 202 points during the first evaluation at a university hospital was then referred to the specialist transplantation hospital, where a second algorithm score was done. The patient final score was 230 of 250 points, thus this patient was qualified for early liver transplantation.

68 (67%) of 102 patients in the early transplantation group had received a liver transplant by the last date of inclusion (June 30, 2016; figure 1). The main reasons why patients were not transplanted were death before or during liver transplantation in 22 (65%) patients and improvement of liver function in seven (21%) patients. During the same period, 129 patients were enrolled to the standard transplantation group, 93 (72%) patients received a liver transplant, and 36 (27%) patients were not transplanted for several reasons (figure 1).

The reproducibility of the selection procedure was assessed for the last seven patients consecutively evaluated in the Lille centre and thereafter by the team at Besançon using a video recording of the consensus meetings. The decision on whether a patient was selected for early liver transplantation or not was the same if the patients evaluated in Lille had been managed in Besançon, with the exception of one patient (inclusion number 01–026). Final scores for each patient are provided in the appendix (appendix p 8). For the patient who had discrepant scores between Lille and Besançon, the difference was only 4 points, and the scores were on the two sides of the 220 point cutoff, which would have resulted in a second discussion to decide whether or not to select the patient.

The characteristics of the patients in the early transplantation and standard transplantation groups at the time of liver transplantation are provided in table 1. As expected, patients from the early transplantation group had more severe liver injury than those in the standard transplantation group.

During the 2 years of follow-up after transplantation, alcohol relapse was observed in 23 (34%) patients in the early transplantation group and 23 (25%) patients in the standard transplantation group. The non-inferiority of early liver transplantation for severe alcohol-related hepatitis versus standard transplantation for end-stage alcohol-related cirrhosis was not established, with an absolute difference of 9·1% (95% CI −∞ to 21·1; p=0·45) in the 2-year rate of alcohol use post-transplant. The corresponding relative risk was 1·45 (95% CI 0·82–2·60)

for the early transplantation group versus the standard transplantation group. Similar results were found in the sensitivity analysis considering death as a competing event (figure 2), with an absolute difference of 8·8% (95% CI –∞ to 20·9) in the cumulative incidence at 2 years.

We observed a higher rate of high alcohol intake after transplantation during the 2 years of follow-up in the early transplantation group (15 [22%] patients), than in the standard transplantation group (five [5%] patients), with an absolute difference of 16·7% (95% CI 5·8–27·6). The corresponding relative risk was 4·10 (95% CI 1·56–10·75). Similar results were found in the sensitivity analysis with death considered a competing event (appendix p 9).

The percentage of time spent consuming any quantity of alcohol was no different between the early transplantation group and the standard transplantation group, with a standardised difference (taking into account patients who did not relapse) of 0·24 (95% CI –0·07 to 0·55; appendix p 11). However, the percentage of time spent consuming a high quantity of alcohol was higher in the early transplantation group than the standard transplantation group; the standardised difference was 0·50 (95% CI 0·17–0·82).

During the 2-year follow-up after transplantation, seven (10%) of 68 patients died in the early transplantation group, and 11 (12%) of 93 patients died in the standard transplantation group (appendix p 9 lists the causes of death). 2-year survival after transplantation was similar in both groups, 89·7% (95% CI 79·6–95·0) in the early transplantation group and 88·2% (79·6–93·3) in the standard transplantation group (HR 0·87 [95% CI 0·33–2·26]; figure 3).

The clinical and biological characteristics of all patients from the early transplantation group, whether transplanted or not, and the not eligible for early transplantation group are described at the time of enrolment in table 2. Patient characteristics between the two groups were well matched. During the 2-year follow-up after enrolment 29 (28%) of 102 patients died in the early transplantation group (22 before liver transplantation and seven after liver transplantation), and 33 (70%) of 47 patients died in the non-eligible for early transplantation group (appendix p 9). 2-year overall survival was 70·6% (95% CI 60·4–78·6) in the early transplantation group, whether transplanted or not, and 28·3% (16·0–41·9) in the non-eligible for early transplantation (HR 0·27 [95% CI 0·16–0·47]; figure 4A). The percentage of days abstinent, was not different between the two groups (81·9% *vs* 88·5%; p=0·16).

101 patients in the early transplantation group of the QuickTrans study were matched to a non-transplanted historical control group. Patient characteristics at the time of non-medical response are reported in the appendix without clinically relevant differences (appendix p 10). The 2-year overall survival in patients with severe alcohol-related hepatitis listed for early liver transplantation was better than the 2-year overall survival in matched controls (70·6% [60·4–78·5] *vs* 18·2% [11·2–26·5]; HR 0·21 [0·13–0·32]), confirming the positive influence of early liver transplantation on 2-year survival (figure 4B).

	Early transplantation group (n=102)	Not eligible for early transplantation group (n=47)
Age, years	55 (45–59)	53 (46–59)
Gender		
Male	69 (68%)	32 (68%)
Female	33 (32%)	15 (32%)
Ascites, any grade	71/100 (71%)	31/44 (70%)
Encephalopathy	18/100 (18%)	8/45 (18%)
Patient treated with corticosteroids	97 (95%)	46 (98%)
INR*	2·2 (2·0–2·9)	2·3 (1·9–2·7)
Bilirubin, mg/dL†	21·8 (14·5–26·8)	21·2 (14·9–27·4)
Serum creatinine, mg/dL‡	0·8 (0·6–1·4)	0·8 (0·6–1·2)
Albumin, g/L§	24 (21–28)	24 (22–28)
AST, IU/L¶	120 (83–162)	119 (85–163)
MELD score‖	29 (26–33)	28 (25–31)
Maddrey's discriminant function**	83 (63–107)	84 (63–99)
Lille score	0·86 (0·65–0·96)	0·79 (0·56–0·88)

Data are median (IQR), n (%), or n/N (%). INR=International Normalised Ratio. AST=aspartate aminotransferase. MELD=Model for End-stage Liver Disease. *Three missing values for INR (n=1 in the not eligible for early transplantation group). †One missing value for bilirubin (n=1 in the not eligible for early transplantation group). ‡Four missing values for creatinine (n=1 in the not eligible for early transplantation group). §32 missing values for albumin (n=12 in the not eligible for early transplantation group). ¶Seven missing values for AST (n=3 in the not eligible for early transplantation group). ‖One missing value for MELD score (n=0 in not eligible for early transplantation group). **Two missing values for Maddrey's discriminant function (n=1 in the not eligible or early transplantation group).

Table 2: **Patient characteristics of the early transplantation group and the not eligible for early transplantation group when medical treatment was initiated in the QuickTrans study**

Discussion

The proportion of patients who had alcohol relapse after transplantation was 34% in the early transplantation group compared with 25% in the standard transplantation group (absolute difference 9·1% [95% CI –∞ to 21·1]); non-inferiority was not proven based on a prespecified margin of 10%. The therapeutic strategy of early liver transplantation resulted in an approximately four times improvement in 2-year overall survival compared with patients not eligible for early transplantation. High alcohol intake was more frequent after early liver transplantation than after standard transplantation. The 2-year survival of patients who had early liver transplantation was similar to that of patients who had standard transplantation. Patients in the present study underwent an initial selection process in primary and secondary centres before inclusion into the study; thus, the percentage of patients finally listed for

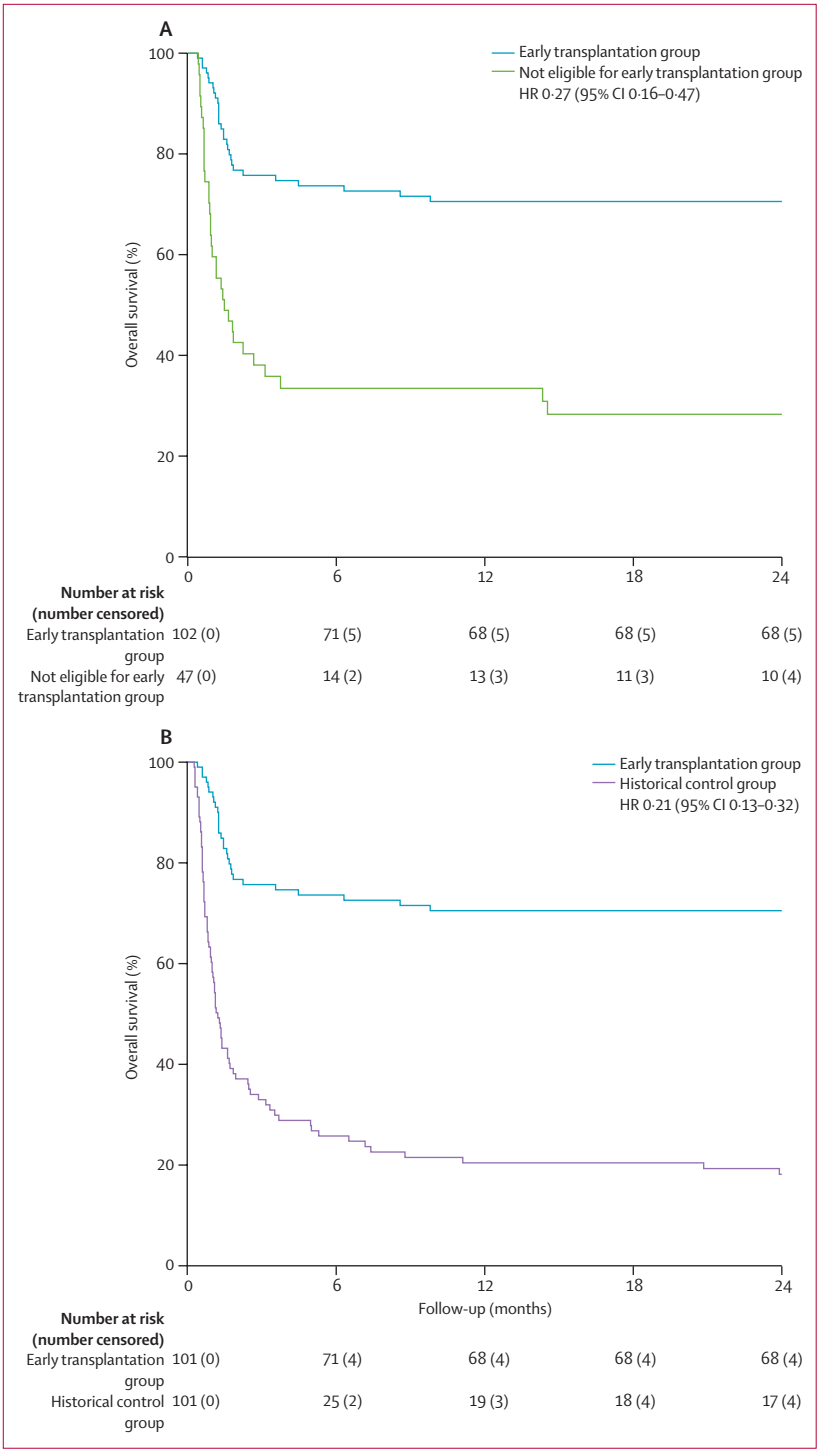

Figure 4: **2-year overall survival in patients with severe alcohol-related hepatitis after no response to medical treatment**

(A) Survival comparison between all the patients in the early transplantation group and all the patients not eligible for early liver transplantation. (B) Survival comparison between all the patients listed for early liver transplantation and the historical controls.

early liver transplantation on the basis of the algorithm does not reflect the percentage of all patients with severe alcohol-related hepatitis who will be put on the waiting list for early liver transplantation.

To our knowledge, this is the first study of liver transplantation that prospectively recorded alcohol consumption using the TLFB instrument, a validated tool to assess efficacy outcomes in alcohol use disorder pharmacotherapy trials.[17–23] The rates of alcohol consumption after transplantation in the early and standard transplantation groups were higher than expected and higher than the estimated rates that were used to calculate the sample size. Previous studies might have underestimated alcohol relapse because of the lack of systematic and prospective follow-up with reliable tools to quantify alcohol consumption. In the present study, the TLFB tool might have identified cases of alcohol relapse that would have remained unidentified without this tool. Although the study design was based on the TLFB tool, we cannot exclude that the rates of relapse might have been higher if biochemical tests such as a phosphatidylethanol blood test had been used.

The study design provides a better understanding of alcohol relapse. Patients who received an early liver transplantation do not resume alcohol consumption earlier than their controls; however, high alcohol intake was more frequent in patients who underwent early transplantation (65%) than in those selected after 6 months of abstinence (22%). Alcohol relapse is a complex issue to analyse using a simple, binary approach (ie, relapse *vs* no relapse). The US National Institute on Alcohol Abuse and Alcoholism has proposed other endpoints to analyse alcohol use after transplantation, such as percentage of days abstinent and percentage of days heavy drinking.[24–27] Using these endpoints, the time spent consuming alcohol, assessed by the percentage of days abstinent, was not different between the two groups, which raises the issue of the ideal definition of abstinence in terms of association with patient outcomes and harm reduction.

Time spent drinking a high quantity of alcohol might be an important variable associated with the development of injury to the liver graft. We suggest that new endpoints be used to investigate whether reducing alcohol intake, even without total abstinence, results in a decrease in overall morbidity and mortality. After liver transplantation, the quantity of alcohol intake is a key factor in graft function and long-term liver-related deaths; therefore, studies could use new endpoints such as a reduction of at least two levels in the WHO risk score from very high to medium risk[21,26] or from high to low risk, which has been classified as a relevant endpoint by the European Medicines Agency. To evaluate the reduction of alcohol intake, endpoints such as days spent abstinent and days of heavy drinking could be used.[21,26] Additional studies are required to explore the

relevance of these endpoints after liver transplantation. Moreover, addiction management was not prespecified by the study protocol and was centre based. An integrative approach to test specific strategies to reduce alcohol relapse should be assessed.[14]

The present study shows the important benefit of early liver transplantation to survival in patients with severe alcohol-related hepatitis at a therapeutic end. Early liver transplantation is the only therapeutic approach that reduces 6-month mortality from approximately 70% to 10%.[1,3–5,14] Considering there are organ shortages for transplantation, some experts fear that if mortality after liver transplantation is too high, this could lead to loss of grafts; however, despite a higher MELD score in early transplant candidates than in standard transplant candidates, the similar survival after transplantation between patients who received early liver transplantation for severe alcohol-related hepatitis and patients who received standard transplantation does not support this theory.

Based on our initial experience in the pilot study,[3] where patients were selected on the basis of predefined criteria, we felt that a fairer and more transparent early transplantation selection process was needed. Thus, the physicians involved in the selection of patients in the pilot study developed a specific algorithm to select patients for early liver transplantation. While this medical decision should be as objective as possible, we felt that the selection should also include a subjective item. This study was not powered to address the reproducibility of the score. Nevertheless, we observed good agreement between the Lille and Besançon teams on the numerical value of the score and the final transplantation decision, suggesting the decision on liver transplantation would be similar regardless of the location the patient is managed at. Further studies are required to validate this algorithm, but we feel that it can contribute to fairer selection in early liver transplantation.[28]

In conclusion, the present study did not establish the non-inferiority of early liver transplantation for severe alcohol-related hepatitis with regards to alcohol relapse after transplantation, and confirms the important survival benefit related to early liver transplantation for severe alcohol-related hepatitis. The study also proposes a reproducible approach to select patients for early liver transplantation. Further progress is required to improve addiction management after liver transplantation.

Contributors

AL, JL, AD, and PM contributed to the study design. JL and AD contributed to the statistics. AL, JL, AD, and PM contributed to the data analysis, data interpretation, and writing of the manuscript. AL, CM, CV, RM, CF, JD, G-PP, CB, FC, CD, DT, VLe, NC, ES, RA, JG, JD, CS, VLu, GL, SD, EN-K, DS, BR, and PM contributed to patient enrolment and data collection. AL, JL, AD, and PM verified the underlying data. All authors had access to the data and responsibility for the decision to submit for publication.

Declaration of interests

The authors declare no competing interests.

Data sharing

Individual patient data will not be available. There are no shared data available. The study protocol is available to download from the ClinicalTrial.gov website.

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