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ORIGINAL ARTICLE

Liver transplantation for severe alcoholic hepatitis: A multicenter Italian study

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There is increasing evidence that early liver transplantation (eLT), performed within standardized protocols can improve survival in severe alcoholic hepatitis (sAH). The aim of the study was to assess outcomes after eLT for sAH in four Italian LT centers and to compare them with non-responders to medical therapy excluded from eLT. Patients admitted for sAH (2013–2019), according to NIAAA criteria, were included. Patients not responding to medical therapy were placed on the waiting list for eLT after a strict selection. Histological features of explanted livers were evaluated. Posttransplant survival and alcohol relapse were evaluated. Ninety-three patients

Abbreviations: AH, alcoholic hepatitis; eLT, early liver transplantation; LT, liver transplantation; sAH, severe alcoholic hepatitis.

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with severe AH were evaluated (65.6% male, median [IQR] age: 47 [42–56] years). Forty-five of 93 patients received corticosteroids, 52 of 93 were non-responders and among these, 20 patients were waitlisted. Sixteen patients underwent LT. Overall, 6-, 12-, and 24-month survival rates were 100% significantly higher compared with non-responders to medical therapy who were denied LT (45%, 45%, and 36%; $p < .001$). 2/16 patients resumed alcohol intake, one at 164 days and one at 184 days. Early LT significantly improves survival in sAH non-responding to medical therapy, when a strict selection process is applied. Further studies are needed to properly assess alcohol relapse rates.

KEYWORDS
alcoholism and substance abuse, clinical decision-making, clinical research/practice, liver transplantation/hepatology

1 | INTRODUCTION

Alcoholic hepatitis (AH) is a clinical syndrome characterized by acute onset of jaundice, PT prolongation, and mild to moderate increase of transaminases in patients with excessive alcohol intake.[1]

An increasing incidence of hospitalization for AH has been seen both in the United States[2] and Europe, with a parallel increase in mortality rates in recent years.[3]

Severe cases (Maddrey Discriminant Function ≥32) not responding to corticosteroid therapy according to the Lille score (REF) present a 6-month mortality rate of 75%.[4] However, despite the lack of effective therapies and high mortality rates, AH has long been considered an absolute contraindication to liver transplantation (LT) by most transplant centers worldwide, mainly due to the lack of pre-transplant abstinence and the potential high risk of posttransplant alcohol relapse.[4–7]

In 2011, a multicenter Franco-Belgian study provided a first answer to these questions, demonstrating that early LT, if performed under stringent selection criteria, significantly increases survival rates in patients with sAH not responding to steroid therapy when compared with patients with sAH who were denied LT.[8]

Since then, only one other multicenter study has been published.[9] This retrospective study, performed among 12 US LT centers, confirmed the high survival rates after early LT for sAH (94% and 84% at 1 and 3 years) with rates of sustained alcohol relapse of 11% at a median follow-up of 1.6 years.

The proposed extension of transplant access for patients with sAH not responding to steroid therapy has raised a heated debate in the world of transplants.[10–13] The core of the controversy is whether it is fair to allocate a precious and limited resource such as an organ to patients who have not demonstrated a period of alcohol abstinence.[14] The main concern is that these patients may resume high posttransplant alcohol consumption, causing loss of the organ, with possible consequent damage to other patients on the waiting list and a potential loss of credibility for the entire organization in the public eye, which could negatively affect the willingness to donate organs.

In Italy, no studies have so far been published on liver transplants for patients with sAH, however, recommendations from an expert panel of transplant hepatologists, appointed by the Italian Association for the Study of the Liver (AISF), stated that patients with sAH, as a first episode of decompensation in chronic liver disease and with adequate psychological/psychiatric undertaking can only be considered for LT if the following conditions are met: total consensus of the paramedical and medical staff, no comorbidities, social integration, supportive family members, psychiatric assessment, and addiction profile.[15]

Therefore, the aim of this study was to assess outcomes after LT for sAH in four Italian LT centers and compare them with those of patients with sAH not responding to medical therapy excluded from LT.

2 | METHODS

2.1 | Study population

Four Italian liver transplant centers provided data on all patients with sAH from January 2013 to September 2019. Inclusion criteria were age above 18 years, clinically diagnosed severe AH,[16] sAH as first episode of liver decompensation, no response to medical therapy (Lille score >0.45). The severity of AH was assessed using the Maddrey Discriminant Function, with patients having a score ≥32 being classified as severe. The Lille score was calculated for all patients. If they received corticosteroid therapy, the Lille score was calculated at day 7 from initiation of corticosteroids; if corticosteroids were not given, the Lille score was calculated at day 7 from initial hospitalization for AH.

The use of corticosteroid therapy was based on clinician decision. Reasons for not using corticosteroids were reported in the clinical chart and recorded. Patients not treated with steroids were treated with standard medical therapy. This included: alcohol abstinence, broad-spectrum antibiotics in patients with suspected infection, and

antibiotic changes according to microbiological results when appropriate, nutritional support to provide adequate protein and calories according to baseline nutritional status and preferably by enteral route. All patients received thiamine. Other vitamin deficiencies were tested and supplemented when needed. Corticosteroids were not administered when active infection or gastrointestinal bleeding was present.

Exclusion criteria were similar to those used in the study by Mathurin et al.[8] and comprised: patient <18-year old and the presence of other liver diseases such as viral hepatitis. Unlike the study by Mathurin et al.[8] and similarly to the one by Lee et al.,[9] patients with previous variceal bleeding were included. Those with controlled or newly diagnosed depression or anxiety disorders were not excluded (Table 1).

For each included patient the following parameters were collected: demographic characteristics (age at admission, gender, ethnicity), severity of liver disease (Maddrey Discriminant Function, Model for End-Stage Liver Disease [MELD], Lille score), medical therapy (use of corticosteroids [yes/no], reasons for not using corticosteroids), illicit substance abuse history and quantification of pre-LT alcohol intake. In patients who underwent LT the following parameters were evaluated: MELD at transplant, patient and graft survival, interval from admission to waiting list (WL) registration, interval from WL registration to LT, posttransplant hospital stay, post-LT alcohol relapse, interval from discharge to alcohol relapse.

Explant histology was assessed in all liver transplanted patients and only those with histological features of AH with or without underlying chronic liver disease were considered for the purpose of this study.

2.2 | Candidate selection

Patients respecting the above-mentioned criteria underwent a strict LT selection process including a dedicated evaluation by an addiction specialist, psychologist, and psychiatrist.

The patient assessment focused on insight into alcohol use disorder, coping skills, and awareness and agreement to adhere to lifelong alcohol abstinence. Quality of affective relationship, presence/absence of caregiver support, good social, and occupational functioning were considered as critical factors. Where available, a neuropsychologist was involved to exclude cognitive impairment related to alcohol when required. The liver transplant selection process was similar to that used in the seminal study by Mathurin et al.[8] (Figure 1).

2.3 | Posttransplant follow-up

After LT, patients underwent standard medical and surgical follow-up.

All transplanted patients received a regular toxicological and psychological evaluation, aimed at supporting motivation and enhancing skills for preventing alcohol relapse. A dedicated "psychosocial team" specialized in addiction medicine worked within the liver transplantation center in close collaboration with the transplant hepatologists/surgeons in order to support and monitor all LT recipients in the follow-up.[17]

Alcohol intake was evaluated during the outpatient clinic with patient and patient's family interviewed and an accurate evaluation of craving as an important predictor of relapse. In two centers, patients with sAH were investigated with a psychopathological scale to support clinical diagnosis (Symptom Checklist-90-R questionnaire) and, when required, with a personality inventory scale (Millon MCMI-II) that includes alcohol abuse and drug abuse scales. In other two centers, before LT all patients were investigated with the AUDIT, CAGE test, and the Alcohol Timeline Followback Method (TLFB), whereas after LT only the TLFB was performed. When required, a neuropsychologist was involved to exclude cognitive impairment related to alcohol.

Patients at higher risk of alcohol relapse received strict psychological and psychiatric surveillance including motivational therapy and involvement of family members with a visit every 2 weeks for the first 6 months post-LT and then a minimum of 1 visit every 3 months in the long-term. One patient received anti-craving medication after liver transplantation with no side effects.

After LT, in order to detect alcohol relapse, besides the use of the dedicated questionnaires and the evaluation of indirect markers of alcohol abuse (MCV, AST, ALT, γ-GT), urinary ethyl-glucuronide was performed every 2 weeks in the first 6 months and then monthly between 6 months and 1 year after transplant and every 3 months thereafter. Ethyl-glucuronide on hair was performed in patients with suspicion or evidence of alcohol relapse.

Any alcohol intake after LT was considered as an alcohol relapse. If a patient lapsed or relapsed after LT, an intensive individual program was initiated. Psychopharmacological interventions to reduce craving were used in selected cases.

Patients with depression and anxiety disorders were treated with antidepressants medication with a good response and tolerance.

2.4 | Statistical analysis

Discrete variables were shown as percentages and parametric variables as mean values ± SD. We used the Chi-square test for the comparison of discrete variables and Student's *t* test for parametric variables, and ANOVA analyses when more than two groups were compared. Differences were considered statistically significant when the *p*-value was less than or equal to .05. Patient and graft survival according to each patient group was evaluated using the life-table method. Comparison between different groups was performed by the log-rank test. Time was measured from the first day of physical presentation to our center to the last known date of follow-up or date of death from any cause. These analyses were performed using SPSS 26.

TABLE 1 Selection criteria and outcomes in studies published on eLT for sAH

Author (year)	Inclusion criteria	Exclusion criteria	1-year survival (%)	Alcohol relapse rate (%)
Mathurin P. (2011) Dharancy S. (2020)	• Non response to medical therapy • Severe AH as the first liver-decompensating event • Presence of close supportive family members • Absence of severe coexisting or psychiatric disorders • Agreement by patients to adhere to lifelong total alcohol abstinence	• Recent infection • Recent gastrointestinal bleeding	82.6%	• Harmful: 10.3%
Im G.Y. (2016)	• Non response to medical therapy • Severe AH as the first liver-decompensating event • Presence of good social support • Favorable psychosocial profile with signed agreement to lifelong alcohol abstinence • Controlled or newly diagnosed depression or anxiety disorders were not excluded • Patients with recent infection and gastrointestinal bleeding were still considered	• Concomitant chronic liver diseases • Concomitant hepatocellular carcinoma • Concomitant HIV • Severe comorbid conditions, or psychiatric disorders	89%	• Any use: 22.2% • Harmful: 11.1%
Weeks S.R. (2018)	• Non response to medical therapy • Presence of insight, commitment to abstinence, and strong social support • Absence of severe comorbid psychiatric or medical disease • Patients with recent infection or gastrointestinal bleeding were not excluded • Patients with history of psychiatric symptoms included if psychiatric assessment demonstrated stably managed disease	• Concomitant presence of other liver disease • Concomitant hepatocellular carcinoma • Patients who received transplants previously	97%	• Any use: 28% • Harmful: 17%
Lee B.P. (2018)	• Age older than 18 years • Clinically diagnosed severe acute AH • No prior diagnosis of chronic liver disease or episodes of AH • Strong social support by family and friends • Absence of severe comorbid medical disorders • Patients with recent infection and gastrointestinal bleeding were still considered • Patient expected to adhere to lifelong alcohol abstinence	• Concomitant presence of other liver disease • HIV • Other contraindications to LT	94%	• Any: 28.3% • Harmful: 11%
Germani G. (2021)	• Age older than 18 years • Clinically diagnosed severe acute AH • Severe AH as the first liver-decompensating event • Strong social support • Absence of severe comorbid medical disorders • Patients with recent infection and gastrointestinal bleeding were still considered • Patient expected to adhere to lifelong alcohol abstinence	• Patient <18 years old • Concomitant presence of other liver disease • HIV	100%	• Any: 12.5%

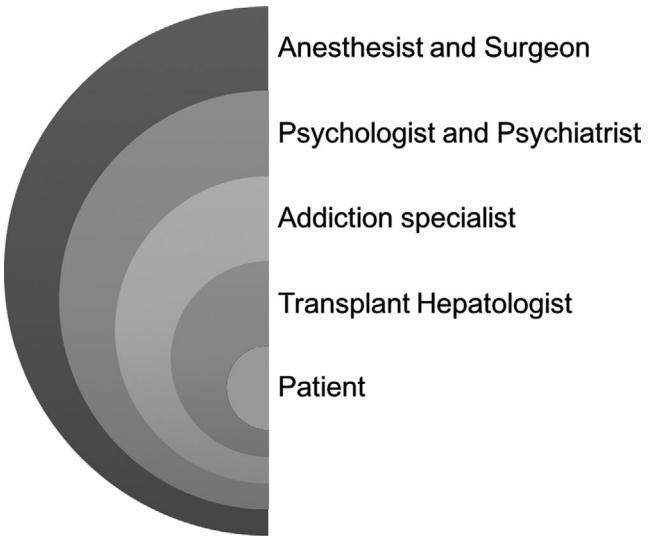


FIGURE 1 Selection process for eLT in patients with sAH

3 | RESULTS

During the study period, a total of 93 consecutive patients admitted for sAH were included (65.6% male, median [IQR] age: 47 [42–56], 97.8% white, and 55.9% referred from another hospital) (Table 1). The median (IQR) alcohol intake was 14 units/day (10–16), with a median (IQR) period of alcohol intake of 20 years (10–30). Fifty-one (54.8%) patients were active smokers and 20 (21.5%) reported use of illicit drugs. An underlying liver cirrhosis was present in 85 (91.4%) patients. At admission, median (IQR) Maddrey's score was 64.5 (45–85), MELD score was 26 (22–31), and MELD-Na was 29 (24–33) (Table 2).

Forty-five of 93 (48.4%) patients received corticosteroid therapy during the study period. Reasons for not giving corticosteroids were confirmed or presumed infection ($n = 28$), severity of liver disease (MELD >25) ($n = 14$), spontaneous clinical improvement ($n = 6$). None received pentoxyphilline. Fifty-two (55.9%) patients were classified as non-responders to medical therapy and underwent the selection process for early LT (Table 2).

Epidemiological characteristics of non-responders were similar to responders apart from the former having significantly more severe disease when measured by Maddrey's score (median [IQR]: 66 [50–90] vs. 59 [41–78]; $p = .04$) and MELD score (median [IQR]: 29.5 [25.2–34.7] vs. 23 [20–26.7]; $p < .001$). This was mainly due to the significant difference in median (IQR) total bilirubin levels between the two groups ($p < .001$) (Table 3). As expected, the median (IQR) Lille score at day-7 in non-responders was 0.9 (0.81–0.97), significantly higher compared to responders. Moreover, the rate of non-responders was significantly higher among patients referred from other hospitals (71.2% vs. 28.8%; $p = .001$) (Table 3).

When only patients treated with steroids were considered ($n = 45$), non-responders had significantly more severe disease when measured by MELD and MELD-Na score (median [IQR]: 28 [24.8–34.5] vs. 20.5 [19–24.8]; $p = .012$ and 29.5 [26–35.2] vs. 23 [20–29]; $p = .02$ respectively). As expected, the median (IQR) Lille score at day-7 in non-responders was 0.87 (0.79–0.97), significantly higher compared to responders ($p < .001$). Moreover, the rate of non-responders was significantly higher among patients referred from other hospitals (65% vs. 25%; $p = .008$) (Table S1).

Among non-responding patients, 20/52 (38.5%) were listed, whereas 32/52 (61.5%) were denied LT for the following reasons: psychosocial/psychiatric ($n = 16$, 50%), death ($n = 6$, 18.7%), clinical improvement during evaluation ($n = 4$, 12.5%), too sick for liver transplantation ($n = 4$, 12.5%), other reasons ($n = 2$, 6.3%). The median (IQR) interval from admission to waiting list (WL) registration was 21 days (8.25–36 days).

Sixteen patients underwent LT, two patients were delisted due to alcohol relapse while on the waiting list, one patient died while on the waiting list and one was still on the waiting list at the time of the study (Figure 2). Median (IQR) MELD score at LT was 32 (25–38), and median (IQR) time from WL registration to LT was 6.5 days (2.25–20) (Table 4).

TABLE 2 Baseline characteristics of study population

	Data
Gender, male, n (%)	61 (65.6)
Age, years, median (IQR)	47 (42–56)
Ethnicity, n (%)	
White	91 (97.8)
Hispanic	2 (2.2)
Referred from another hospital, yes, n (%)	51 (54.8)
First episode of AAH, yes, n (%)	93 (100)
First episode of liver decompensation, yes, n (%)	93 (100)
Alcohol consumption, units/day, median (IQR)	14 (10–16)
Duration of alcohol consumption, years, median (IQR)	20 (10–30)
Active smoker, yes, n (%)	51 (54.8)
Illicit substance abuse, yes, n (%)	20 (21.5)
Underlying cirrhosis, yes, n (%)	85 (91.4)
Received corticosteroids for AH, n (%)	45 (48.4)
Reasons for not using corticosteroids, n (%)	
Presumed/confirmed infection	28 (58.3)
Severity of liver disease (MELD >25)	14 (29.2)
Other	6 (12.5)
WBC, cells/mm^3, median (IQR)	11.6 (7.7–16.7)
INR, median (IQR)	1.9 (1.7–2.4)
Creatinine, mg/dl, median (IQR)	0.9 (0.59–1.9)
Sodium, median (IQR)	134 (127–137)
Aspartate aminotransferase, U/L, median (IQR)	114 (74–157)
Alanine aminostrasferase, U/L, median (IQR)	40 (28–73)
Bilirubin, mg/dl, median (IQR)	19.7 (11.1–26.6)
Maddrey's score, median (IQR)	64.5 (45–85)
MELD score, median (IQR)	26 (22.2–31)
MELD-Na score, median (IQR)	29 (24–33)

TABLE 3 Characteristics of patients with severe AH according to response to medical therapy

	Non-responders $n = 52$	Responders $n = 41$	*p*-value
Gender, male, n (%)	36 (69.2)	25 (61)	.4
Age, years, median (IQR)	46.5 (43–56)	47 (39.5–53.5)	.2
Ethnicity, n (%)			.1
White	52 (100)	39 (95.1)	
Hispanic	0 (0)	2 (4.9)	
Referred from another hospital, yes, n (%)	37 (71.2)	14 (35)	.001
Alcohol consumption, units/day, median (IQR)	15 (8.5–16)	10 (10–20)	.7
Duration of alcohol consumption, years, median (IQR)	20 (11.5–30)	20 (10–30)	.3
Active smoker, yes, n (%)	25 (49)	23 (59)	.3
Illicit substance abuse, yes, n (%)	8 (15.7)	12 (30.8)	.08
Underlying cirrhosis, yes, n (%)	47 (90.3)	38 (92.6)	.4
Received corticosteroids for AH, n (%)	20 (38.5)	25 (61)	.03
Reasons for not using corticosteroids, n (%)			.001
Presumed/confirmed infection	19 (57.6)	10 (62.4)	
Severity of liver disease	13 (39.4)	1 (6.3)	
Other	1 (3)	5 (31.3)	
WBC, cells/mm^3, median (IQR)	11.8 (8.2–17.9)	11.4 (7.1–14.6)	.4
INR, median (IQR)	1.9 (1.7–2.4)	1.8 (1.6–2.3)	.2
Creatinine, mg/dl, median (IQR)	1.12 (0.7–2.7)	0.6 (0.4–1)	<.001
Sodium, median (IQR)	133 (131–137)	135 (130–139)	.5
Aspartate aminotransferase, U/L, median (IQR)	125 (76–156)	96 (67–159)	.6
Alanine aminostrasferase, U/L, median (IQR)	42 (28–73)	40 (28–70)	.9
Bilirubin, mg/dl, median (IQR)	23.5 (17.1–31)	14 (8.5–22.7)	<.001
Maddrey's score, median (IQR)	66 (50–90)	59 (41–78)	.04
MELD score, median (IQR)	29.5 (25.2–34.7)	23 (20–26.7)	<.001
MELD-Na score, median (IQR)	30 (27–34.7)	25 (21.2–29.7)	<.001
Lille score, median (IQR)	0.9 (0.81–0.97)	0.12 (0.04–0.27)	<.001

All 16 patients who underwent LT had available explant histology records, and all of them presented a pattern compatible with AH features on cirrhosis.

3.1 | Outcomes after liver transplantation

Overall, 6-, 12-, 24-, and 36-month survival rates were 100% significantly higher compared with patients with sAH not responding to medical therapy who were denied LT (41%, 41%, 38%, and 35%, respectively; log-rank $p < .001$). Survival after LT was also significantly higher when compared with responders to medical therapy (77%, 67%, 65%, and 65%, respectively; log-rank $p = .008$) (Figure 3). The median (IQR) posttransplant hospital stay was 22.5 days (17–37.5).

One patient died at 31 months after LT due to pulmonary aspergillosis.

After a median (IQR) follow-up of 53.5 months (39–78.7), 2/16 (12.5%) patients resumed alcohol intake, one at 164 days and one at 184 days. Both patients were given counseling by an addiction specialist and psychologist, however, one patient remained a daily consumer and was lost at follow-up. The patient who continued alcohol intake also presented no adherence to immunosuppressive with a progressive increase in liver function test.

3.2 | Outcomes of non-transplanted patients

Among non-responding patients who were denied LT ($n = 36$), 23 patients died and one was lost at follow-up. Non-responding patients who survived the sAH event presented a significantly lower MELD (median [IQR]: 27.5 [24–30.8] vs. 31 [25–36]; $p = .03$) and MELD-Na (median [IQR]: 28.5 [24.5–33.5] vs. 32 [27–36]; $p = .025$) at admission compared to those who died, whereas no differences were seen between the two groups in terms of gender, age at admission, and MELD score.

Among responding patients ($n = 41$), 16 patients died and four were lost at follow-up. Among surviving patients, one underwent LT for the development of hepatocellular carcinoma. Responding patients who

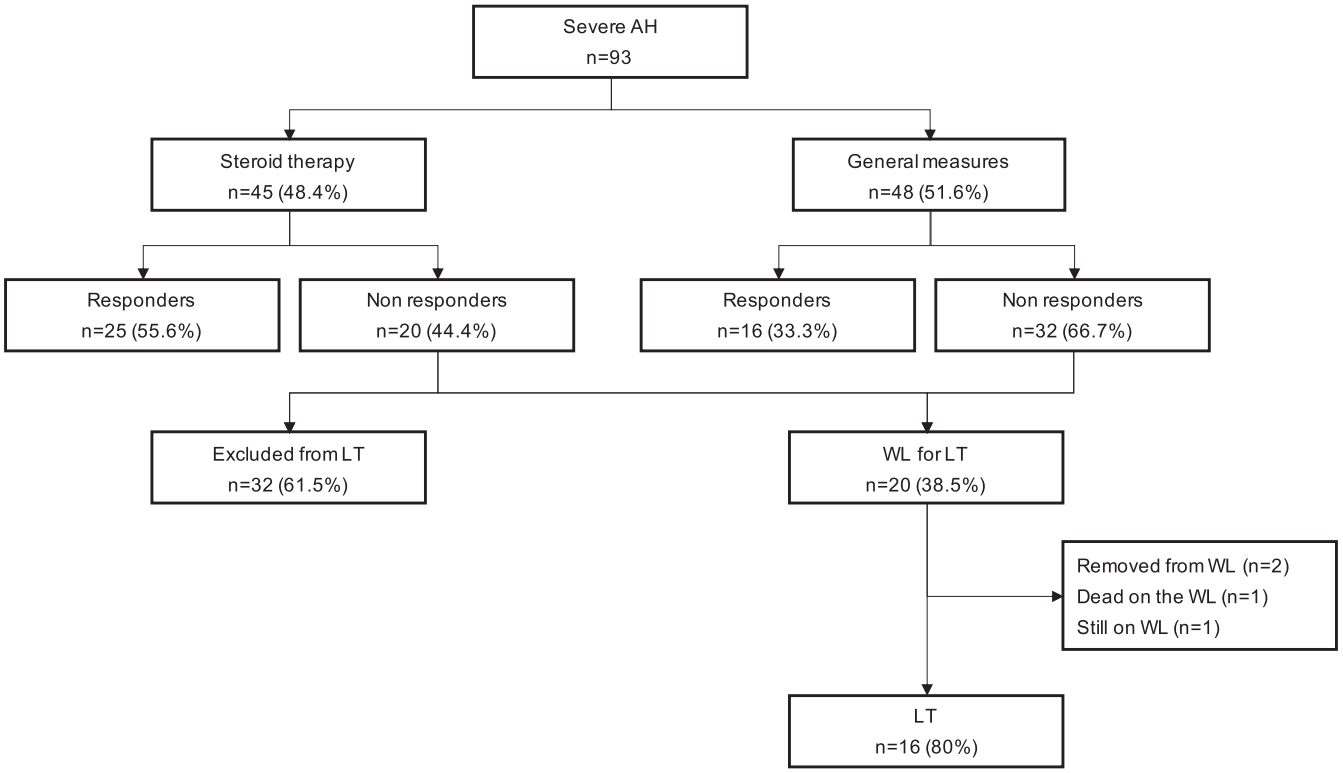


FIGURE 2 Flowchart of the study population

TABLE 4 Characteristics of 16 patients with severe AH who underwent early LT

	Data
Gender, male, n (%)	12 (75)
Age, years, median (IQR)	45 (43–53)
Referred from another hospital, yes, n (%)	11 (68.8)
Alcohol consumption, units/day, median (IQR)	15 (10.5–15.7)
Duration of alcohol consumption, years, median (IQR)	30 (15–30)
Active smoker, yes, n (%)	8 (50)
Illicit substance abuse, yes, n (%)	3 (18.8)
Underlying cirrhosis, yes, n (%)	16 (100)
Received corticosteroids for AH, n (%)	7 (43.8)
MELD score at LT, median (IQR)	32 (25–38)
Interval from admission to WL, days, median (IQR)	21 (8.25–36)
Interval from WL to LT, days, median (IQR)	6.5 (2.25–20)
Post-LT hospital stay, days, median (IQR)	22.5 (17–37.5)
Alcohol relapse after LT, n (%)	2 (12.5)

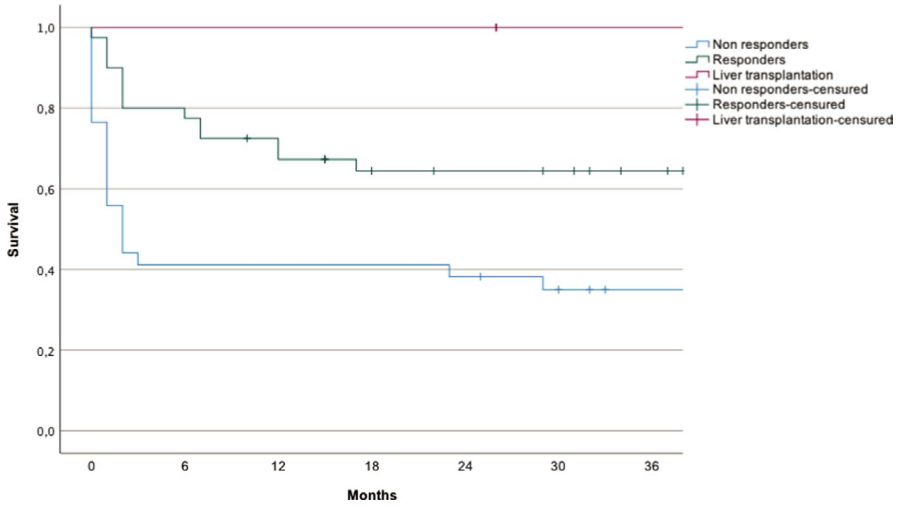
survived the sAH event presented a significantly lower MELD (median [IQR]: 22 [20–24] vs. 26 [21.5–31]; $p = .009$) and MELD-Na (median [IQR]: 23.5 [20.3–25.8] vs. 30 [26.5–32.8]; $p < .001$) at admission compared to those who died, whereas no differences were seen between the two groups in terms of gender or age at admission.

Both non-responding patients who were denied LT and responding patients were offered the same psycho-social management as those placed on the LT waiting list.

4 | DISCUSSION

This study was proposed with the aim of supporting the utility of eLT in patients with sAH on chronic liver disease in Italy, following the example of the colleagues from Lille who first published the 26 cases subjected to eLT[8] and the subsequent study by Lee et al.[9]

Therefore, four transplant centers developed a multicenter study, which represents the first experience of eLT for severe alcoholic



	3 months	6 months	12 months	18 months	24 months	30 months	36 months
Non responders	15	14	14	14	13	11	8
Responders	32	32	28	23	21	20	17
Liver transplantation	16	16	16	16	16	15	15

FIGURE 3 Kaplan–Meier estimates of survival among the 16 liver transplanted patients and in patients with severe alcoholic hepatitis stratified according to the response to medical therapy [Color figure can be viewed at wileyonlinelibrary.com]

hepatitis in Italy, and the second largest case series in Europe after the French one.[8]

A strength of the present study is the homogeneity with which patients were selected,[15] as selection criteria were strictly followed for patients who came to our attention with alcoholic hepatitis developed on pre-existing liver disease. Most of the selection criteria were in line with those reported in the study by Mathurin et al.[8] (Table 1). Therefore, we think that our cases are comparable with the Franco-Belgian series,[8] but more homogeneous compared to the series of the American consortium, where nearly 40% of patients were affected by cirrhosis, without any signs of AAH.[9]

In this study confirmation of acute liver damage on chronic liver disease was obtained from explants at transplant for all cases included.

Certainly, the most favorable data are represented by the survival rates of transplanted patients, which were significantly higher compared to those of the 36 patients who had not responded to therapy and were not considered eligible for transplantation, similarly to what was reported in previous case series[8,9] (Table 1). The survival of patients who underwent eLT was also higher than that reported in 41 patients who had responded to medical therapy and had not been selected for transplant.

One patient died from aspergillus infection at 31 months after transplant, similarly to the four cases reported by Mathurin et al.[8]

An additional singular issue of this study is the conservative use of corticosteroids in patients with sAH. Less than 50% were treated with steroids, significantly lower compared to the rate reported in Mathurin's study (92%). However, our data are similar to those in the US study in that Lee et al.[9] had about 50% of patients with eLT who had been treated with steroids. Although it can be argued that some of the untreated patients would have responded to steroids and thereby avoided eLT, we note that recent studies have challenged the benefit of CS particularly in AH patients with an initial MELD score higher than 25.[18] Moreover, we have interpreted the trend in recent years to use less steroids, at least in Italy, mainly due to the high risk of infections. In this context, the prolonged interval between the occurrence of sAH and admission to the four referral centers and the frequent development of infective complications were the two main reasons for a cautious use of steroids.

Another positive data are the acceptable rate of alcohol relapse after eLT, equal to 12.5% in line with several studies performed in patients transplanted after 6 months of alcohol abstinence before waiting list registration. Although the number of patients receiving LT in our series is small, we are gratified by the low rate of relapse into alcohol consumption after eLT, which in our opinion justifies eLT in these cases. Moreover, one patient who relapsed has already returned to sobriety and we hope this will be confirmed in the future.

When we evaluated the severity of liver disease at transplant, the median MELD was 32, confirming the severity of the disease, and the interval between enrolment and transplant was less than 1 week. It is well known that in such cases a long waiting time can expose the patient to the onset of complications, especially infections and respiratory complications, which could preclude the transplant, or to the worsening of clinical conditions or becoming futile. The high urgency of the intervention therefore has relevant ethical implications that exceed the benefit for the individual patient: The onset of complications and the worsening of clinical conditions that could make the transplant futile would indeed cause the loss of a precious resource such as an organ, which could be used for another patient.

Lastly, the positive and encouraging results of this study have highlighted a decisive aspect for its success. All four transplant centers involved have for years developed a program for the selection of patients with alcohol-related liver disease, based not only on evaluation by the transplant hepatologists, but also in close collaboration with the transplant-dedicated addiction specialists, psychologists, and psychiatrists, specifically prepared and trained for the alcohol problem. We believe that the rigorous selection by the toxicological,

psychological and psychiatric team has undoubtedly identified the patients who could potentially have good adherence to the medical prescriptions after transplantation, as well as the tremendous expertise in alcohol-related diseases in the same centers by the hepatologists, which made a difference.

The data provided by this study confirm the idea that patients with sAH not responding to medical therapy can meet the eligibility criteria for liver transplantation, since they have a high transplant benefit and a low risk of recurrence of posttransplant alcohol consumption. These patients fully satisfy all three criteria used for the selection of candidates eligible for transplantation: urgency, utility, and benefit.[19]

Given the high 6-month mortality rate (approximately 75%) for patients with sAH not responding to medical therapy, this category of patients fully satisfies the urgency criterion, which is always considered a preferential criterion. Similarly, the utility criterion is satisfied as data provided by this study on survival at 24 months after LT are extremely positive and they suggest that the results could be comparable to those of patients with alcoholic cirrhosis who respected the 6-month rule. Lastly, considering the transplant benefit, despite the lack of data on 5-year posttransplant survival,[20] it is clear that LT offers a huge benefit to patients with sAH not responding to medical therapy as the survival differential with and without transplant in shorter time spans is extremely high.

Therefore, should the data be further confirmed, the exclusion from liver transplant of patients with sAH not responding to medical therapy would no longer be ethically justified.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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