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CLINICAL—LIVER

Intensive Enteral Nutrition Is Ineffective for Patients With Severe Alcoholic Hepatitis Treated With Corticosteroids

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BACKGROUND & AIMS: Severe alcoholic hepatitis (AH) is a life-threatening disease for which adequate oral nutritional support is recommended. We performed a randomized controlled trial to determine whether the combination of corticosteroid and intensive enteral nutrition therapy is more effective than corticosteroid therapy alone in patients with severe AH. **METHODS:** We enrolled 136 heavy consumers of alcohol (age, 18–75 y) with recent onset of jaundice and biopsy-proven severe AH in our study, performed at 18 hospitals in Belgium and 2 in France, from February 2010 through February 2013. Subjects were assigned randomly (1:1) to groups that received either intensive enteral nutrition plus methylprednisolone or conventional nutrition plus methylprednisolone (controls). In the intensive enteral nutrition group, enteral nutrition was given via feeding tube for 14 days. The primary end point was patient survival for 6 months. **RESULTS:** In an intention-to-treat analysis, we found no significant difference between groups in 6-month cumulative mortality: 44.4% of patients died in the intensive enteral nutrition group (95% confidence interval [CI], 32.2%–55.9%) and 52.1% of controls died (95% CI, 39.4%–63.4%) ($P = .406$). The enteral feeding tube was withdrawn prematurely from 48.5% of patients, and serious adverse events considered to be related to enteral nutrition occurred in 5 patients. Regardless of group, a greater proportion of patients with a daily calorie intake less than 21.5 kcal/kg/day died (65.8%; 95% CI, 48.8–78.4) than patients with a higher intake of calories (33.1%; 95% CI, 23.1%–43.4%) ($P < .001$). **CONCLUSIONS:** In a randomized trial of patients with severe AH treated with corticosteroids, we found that intensive enteral nutrition was difficult to implement and did not increase survival. However, low daily energy intake was associated with greater mortality, so adequate nutritional intake should be a main goal for treatment. ClinicalTrials.gov number: NCT01801332.

Keywords: Nutrients; Ethanol; Liver Disease; Cirrhosis.

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Abbreviations used in this paper: **AH, alcoholic hepatitis; ALD, alcoholic liver disease; BMI, body mass index; BW, body weight; CI, confidence interval; DF, Maddrey's discriminant function; HRS, hepatorenal syndrome; MELD, model for end-stage liver disease; SHR, subdistribution hazard ratio.**

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CLINICAL LIVER

Alcoholic hepatitis (AH) is a clinical syndrome characterized by the recent onset of jaundice in patients with ongoing alcohol abuse.[1] Histologically, AH is defined by steatosis, hepatocyte ballooning, and an inflammatory infiltrate with polymorphonuclear neutrophils. Severe AH is commonly defined by a Maddrey's discriminant function (DF) of 32 or higher.[2] This severe form, which occurs predominantly on a background of cirrhosis, is associated with a poor short-term prognosis and a 3-month mortality rate of 30%–50%.[3] European and US guidelines for alcoholic liver disease (ALD) recommend the use of corticosteroids or pentoxifylline in patients with severe AH.[4,5] A meta-analysis using individual patient data from 5 recently published randomized controlled trials showed that 28-day survival rates were higher for corticosteroid-treated patients than for non–corticosteroid-treated patients.[6] A survival benefit also was observed at 1 month for corticosteroid treatment vs placebo after adjustments for baseline determinants of prognosis in the largest randomized controlled trial in severe AH to date.[7] The applicability of corticosteroid therapy is limited by concerns about the risks of sepsis and gastrointestinal bleeding, and its benefits after 1 month are controversial.[4,7] Nevertheless, regardless of the therapeutic strategy, the 6-month mortality rate remains high, and current available treatments are unsatisfactory.

Malnutrition is associated commonly with cirrhosis and its severity.[8] In severe AH, several studies have highlighted that protein energy malnutrition is present in almost every patient, and is associated with impaired survival.[9] Some investigators have proposed that the presence of malnutrition on a background of chronic alcohol consumption could foster hepatic injury.[9,10] The European Society for Clinical Nutrition and Metabolism guidelines recommend a daily energy intake of 35–40 kcal/kg of body weight (BW) and a daily protein intake of 1.2–1.5 g/kg of BW in patients with liver disease.[11] However, these objectives often are difficult to achieve in clinical practice, especially in this severely ill population. Therefore, the use of tube feeding is strongly recommended if patients are not able to maintain adequate oral intake.[11] Only 2 randomized trials comparing an enteral diet with a control diet in patients with AH have been published to date. The first one compared a controlled diet with a supplemented diet in 64 patients with AH, and did not observe any effect on clinical outcome.[12] However, this trial was not restricted to patients with severe AH and patients did not receive corticosteroids. The second trial compared 28 days of total enteral nutrition with corticosteroid treatment in 71 patients with severe AH and showed that these approaches resulted in comparable 1- and 6-month survival rates.[13] Another study reported that aggressive nutritional intervention may accelerate liver function improvement in ALD,[14] and, more recently, a meta-analysis suggested that nutritional therapy may have beneficial effects on survival in alcoholic cirrhosis and AH.[15] This meta-analysis did not report a significant benefit of an enteral over parenteral route of administration. However, the possible complementary effects of combining enteral nutrition with corticosteroid treatment have never been studied in a randomized controlled trial. Moreover, the optimal energy intake to target in severe AH patients remains unknown. The aim of this randomized controlled trial was to evaluate the impact of corticosteroid plus intensive enteral nutrition therapy compared with corticosteroid therapy alone on 6-month prognosis (mortality and severe complications of cirrhosis) in patients with severe AH.

Materials and Methods

Study Design

This multicenter randomized controlled clinical trial was performed in 18 Belgian and 2 French hospitals. The study was approved by the ethical Committee of CUB Hôpital Erasme and by the local institutional review board or ethics committee at each participating hospital. All co-authors had access to the study data and reviewed and approved the final manuscript. This clinical trial is registered on ClinicalTrials.gov (number: NCT01801332).

Patients

Eligible patients were aged 18 to 75 years, were chronic alcohol consumers (>40 g/day), had a recent onset of jaundice within the past 3 months, had biopsy-proven alcoholic hepatitis, and had a DF of at least 32.[2] The delay between admission and randomization was no longer than 14 days. Histologic confirmation of AH was based on the following findings: ballooned hepatocytes, Mallory bodies, and infiltration of polymorphonuclear neutrophils. Exclusion criteria included the presence of hepatitis B surface antigen, human immunodeficiency virus antibodies, chronic hepatitis C infection, severe concurrent disease that compromised 6-month survival, uncontrolled bacterial or fungal infection (infection had to be judged under control for at least 3 days), uncontrolled upper gastrointestinal bleeding (bleeding had to be under control for at least 5 days), type 1 hepatorenal syndrome (HRS), history of bariatric surgery, pentoxifylline, or molecular adsorbent recirculating system therapy. Written informed consent was obtained from all participants. Approval was given by a relative in the case of significant encephalopathy.

Randomization

Eligible patients were assigned randomly at a 1:1 ratio to receive both intensive enteral nutrition and methylprednisolone (intensive arm), or conventional nutrition and methylprednisolone (control arm). Randomization was centralized (CUB Hôpital Erasme) and patients were assigned in blocks of 6 (sealed opaque envelopes) without stratification. Both patients and investigators were aware of treatment assignment.

Procedures

Methylprednisolone was given at a dose of 32 mg/day for 28 days in both groups. Patients randomized to the intensive arm received Fresubin HP Energy Fresenius Kabi (Schelle, Belgium) (composition per 1000 mL: 1500 kcal, 75 g protein, 170 g carbohydrates, 58 g fat, 790 mL water) using a feeding tube for 14 days, according to the following protocol: 1000 mL/day if BW was less than 60 kg, 1500 mL/day if BW was

between 60 and 90 kg, and 2000 mL/day if BW was more than 90 kg. Patients in the intensive arm also were allowed to have additional oral nutritional intake. Patients randomized to the control arm received conventional nutrition according to local practice. Daily energy intake (in kcal/day and in kcal/kg/day, recorded as a continuous variable and after categorization into tertiles) and protein intake were recorded by a dietician for 14 days, at least 3 times a week for both groups. Age, sex, body mass index (BMI), presence and grade of encephalopathy and ascites, blood cell count (leukocytes, neutrophils, and platelets), prothrombin time, international normalized ratio, bilirubin level, albumin, serum sodium, serum creatinine, urea, aspartate aminotransferase, and model for end-stage liver disease (MELD) score[16] were assessed at screening and baseline. Liver imaging was performed at screening. Apart from BMI and serum albumin level, no specific pretreatment assessment of nutritional state was conducted before randomization. Clinical follow-up and laboratory analyses were performed on day 7, day 14, day 28, and then monthly up to month 6. Alcohol relapse was evaluated by patients' self-reporting at each follow-up visit. Corticosteroid treatment response was calculated using the Lille model 7 days after treatment had been initiated.[17] Early discontinuation of corticosteroids according to the Lille score was left to the discretion of the investigator.

Outcomes

The primary end point was mortality at 6 months after initiation of therapy. Secondary end points included mortality at 1 month, occurrence of infection, and occurrence of HRS (defined according to recommended international criteria[18]) 6 months after beginning treatment.

Statistical Analysis

Variables with normal distribution are presented as means ± SD. Skewed variables are presented as medians with interquartile ranges. Categoric variables were analyzed using the Pearson chi-square test or the 2-sided Fisher exact test, whereas quantitative variables were assessed using the Student *t* test or the Mann–Whitney test when appropriate. Follow-up time was defined as the period from the first day of initiation of therapy to 180 days after treatment started. Study outcomes were evaluated using a multistate model (variables were coded 0 if the patient was censored alive, 1 for the occurrence of the event of interest, and 2 in the case of the occurrence of a competing risk as defined later) as recommended in cirrhotic patients.[19] Data for patients who had not died were censored at the date of the last follow-up visit. In this survival analysis, liver transplantation was considered to be a competing risk event as recommended.[19] A cumulative incidence function of death was calculated to describe the probability of death at a given time and is reported at 6 months with a 95% confidence interval (95% CI). The equality of cumulative incidence functions for a given prognostic factor was assessed using Gray's[20] test.

The occurrence of HRS and infection was evaluated using cumulative incidence functions as mentioned earlier and baseline characteristics of patients were compared according to the presence or absence of these events. In these later analyses, death or liver transplantation without HRS or without the presence of infection was considered to be a competing event. Sites and number of infections were compared according to therapy group.

A per-protocol analysis comparing patients who managed to retain their feeding tube for 14 days in the intensive compared with the control arm also was conducted.

Finally, 3 post hoc analyses were performed. First, the association between daily calorie intake (after stratification into tertiles) and 6-month mortality was assessed. Univariate and multivariable regression analyses were conducted using the Fine and Gray[21] proportional hazards models to identify prognostic factors at baseline associated with 6-month mortality. Subdistribution hazard ratios (SHRs) were reported with 95% CIs. Factors included in a composite score were not included in multivariable analysis to avoid bias related to the effect of collinearity.[22] Only covariates with a *P* value of less than .10 in the univariate analysis were included in the multivariable model. The proportional subhazards assumption was assessed using interaction terms with time.[23] Second, a similar approach was used to identify prognostic factors associated with premature withdrawal of the feeding tube in the intensive enteral therapy group. In this later analysis, death before the planned 14 days of enteral nutrition was considered as a competing event. Third, patients allocated to the intensive and the control arms were compared according to daily nutritional intake.

The sample size was calculated based on the following hypotheses: with an expected mortality rate of 50% at 6 months in the control group (ie, not receiving intensive enteral nutrition) based on a previous study in Belgium,[24] the intervention would lead to a mortality rate of 25% at 6 months. Using a type I error rate of 5%, a power of 80%, and a 2-sided test with a continuity correction, at least 132 patients were required for the study. The potential heterogeneity in the treatment effect according to different study centers was tested by adding an interaction center × treatment in a Cox model. All the statistical tests used were 2-tailed, and a *P* value less than .05 was considered statistically significant. A Bonferroni correction was applied to *P* values when multiple comparisons were performed. Statistical analyses were performed using STATA/IC 13.0 for Windows (StataCorp LP, College Station, TX) and *R* 3.1.0 (*R* Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org) software.

Results

Patients

A total of 208 patients were screened between February 8, 2010, and February 18, 2013, for inclusion in the study. Of these, 136 met criteria for inclusion and were enrolled in the study (68 were randomized to each therapy group). Supplementary Figure 1 shows the disposition of patients throughout the study. Three patients were lost to follow-up evaluation. Two patients in the control group underwent early liver transplantation at 20 and 45 days for nonresponse to corticosteroid therapy (Lille score, 0.899) and severe worsening of liver function despite initial response to treatment (Lille score, 0.008), respectively.[25]

The baseline characteristics of the 136 randomized patients are shown in Table 1. The daily calorie (total and per kg/BW), protein, carbohydrate, and lipid intake for both groups is shown in Table 2. With the exception of carbohydrates (254 ± 88 vs 218 ± 114 g/day; $P = .073$), which did not reach the conventional statistical threshold, all nutrient intake factors were significantly higher in the intensive arm.

Table 1. Baseline Characteristics of Patients Included in the Intention-to-Treat Analysis

Characteristics	Intensive enteral nutrition arm (n = 68)	Missing data, n (%)	Control arm (n = 68)	Missing data, n (%)	*P*
Age, *y*	49.5 ± 8.7	0	51.5 ± 8.6	0	.191
Male sex, n (%)	47 (69.1)	0	40 (58.8)	0	.211
BMI, kg/m^2	26.7 ± 6.2	4 (5.9)	27.0 ± 5.8	2 (2.9)	.813
Ascites, n (%)	47 (69.1)	0	48 (70.6)	0	.582
Ascites, n (%)		0		0	
Grades 0–1	23 (33.8)		22 (32.4)		
Grade 2	31 (45.6)		33 (48.5)		.941
Grade 3	14 (20.6)		13 (19.1)		
Encephalopathy, n (%)	27 (39.7)	0	20 (29.9)	1 (1.5)	.229
Grade 0	41 (60.3)		47 (70.2)		
Grade I	15 (22.1)		7 (10.4)		.187
Grades II–III	12 (17.7)		13 (19.4)		
INR	1.8 (1.6–2.1)	0	1.8 (1.6–2.1)	0	.934
Platelets, $\times 10^3/\mu L$	116 (74–195.5)	0	110 (75–185)	1 (1.5)	.773
Bilirubin level, *mg/dL*	13.3 (9.2–23.4)	0	11.9 (7.0–21.4)	0	.146
Creatinine level, *mg/dL*	0.8 (0.6–1.0)	0	0.7 (0.5–0.9)	0	.105
Albumin level, *g/dL*	2.6 (2.3–2.9)	4 (5.9)	2.5 (2.2–2.8)	4 (5.9)	.505
Sodium level, *mEq/L*	134 (131–138)	0	135 (133–138)	2 (2.9)	.266
AST level, *U/L*	125.5 (87.5–176.5)	0	114.0 (83.0–148.0)	0	.184
Leukocytes, $/\mu L$	8950 (6480–11,400)	1 (1.5)	9000 (6600–12,300)	1 (1.5)	.908
Neutrophils, $/\mu L$	6328.5 (3922–8770)	2 (2.9)	6020 (4500–8348.5)	8 (11.8)	.978
MELD	22.8 (21.4–26.3)	0	22.3 (20.2–24.9)	0	.113
DF	52.3 (40.9–70.2)	0	53.9 (41.1–66.0)	0	.826

NOTE. Variables with normal distribution are presented as means ± SD. Skewed variables are presented as median (interquartile range).
AST, aspartate aminotransferase; INR, international normalized ratio.

Efficacy

There was no significant difference in cumulative risk of mortality at 6 months between the 2 groups in the intention-to-treat analysis (44.4%; 95% CI, 32.2–55.9 in the intensive arm, vs 52.1%; 95% CI, 39.4–63.4 in the control arm; $P = .406$) (Figure 1). There was no significant treatment effect interaction between centers ($P = .194$).

Thirty deaths occurred in the intensive arm and 35 deaths occurred in the control arm. There was no significant difference in cumulative 1-month mortality between the intensive enteral nutrition group and the control group (16.2%; 95% CI, 8.6%–25.9% vs 20.7%; 95% CI, 11.9–31.1; $P = .534$) (Supplementary Figure 2).

In the per-protocol analysis, there was neither a significant difference in cumulative risk of mortality at 6 months between the 2 groups (37.4%; 95% CI, 21.5–53.3 in the intensive arm, vs 52.1%; 95% CI, 39.4–63.4 in the control arm; $P = .138$) (Supplementary Figure 3) nor at 1 month (5.7%; 95% CI, 1.0–16.9 vs 20.7%; 95% CI, 11.9–31.0; $P = .051$) (Supplementary Figure 4).

There was no significant difference in the incidence of HRS during the study period between the intensive enteral nutrition arm compared with the control arm in the intention-to-treat analysis (21.3%; 95% CI, 12.3–31.9 vs 15.8%; 95% CI, 8.0–25.9; $P = .437$) (Supplementary Figure 5). Data were missing for 4.4% of patients (6 died of an unknown cause without a prior episode of HRS). There was also no significant difference between the intensive and control arms in cumulative incidence of hepatorenal syndrome at 6 months in the per-protocol analysis (29.4%; 95% CI, 15.1–45.2 vs 15.8%; 95% CI, 8.0–25.9; $P = .125$) (Supplementary Figure 6).

Table 2. Daily nutritional intake according to group allocation

	Intensive enteral nutrition (n = 68)	Missing data, n (%)	Control group (n = 68)	Missing data, n (%)	*P*
Total kcal/day	2206 ± 754	6 (8.8)	1754 ± 656	6 (8.8)	.001
Total kcal/kg/day	27.9 ± 8.9	6 (8.8)	23.3 ± 10.0	6 (8.8)	.008
Proteins, *g/day*	106 ± 37	11 (16.1)	80 ± 32	12 (17.6)	.0001
Carbohydrates, *g/day*	254 ± 88	12 (17.6)	218 ± 114	22 (32.4)	.073
Lipids, *g/day*	86 ± 31	12 (17.6)	71 ± 29	22 (32.4)	.013

NOTE. Variables are presented as means ± SD.

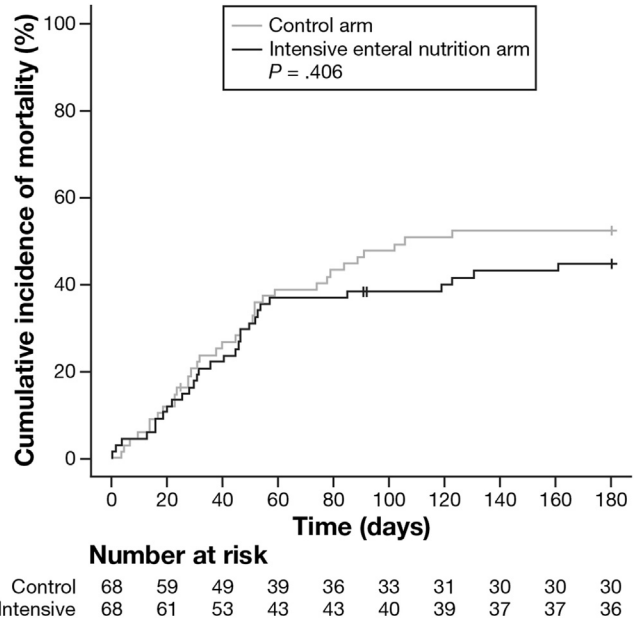

Figure 1. Cumulative incidence of 6-month mortality according to intervention group. There was no significant difference in the cumulative risk of mortality at 6 months between the intensive and the control arm in the intention-to-treat analysis (44.4%; 95% CI, 32.2–55.9 in the intensive arm, vs 52.1%; 95% CI, 39.4–63.4 in the control arm; $P = .406$).

There was no significant difference for the occurrence of at least one infection during the study period between the intensive enteral nutrition group compared with the control arm (60.6%; 95% CI, 47.7–71.2 vs 62.2%; 95% CI, 49.0–72.9; $P = .652$) (Supplementary Figure 7). Data were missing for 2.2% of patients (3 died of an unknown cause without a prior episode of infection). Along the same line, the distribution of the types of infections (ie, pneumonia, spontaneous bacterial peritonitis, urinary tract infections, bacteremia, and other infections), as well as the total number of infections, did not differ significantly between the 2 groups ($P = .888$). Similarly, the incidence of infection at 6 months did not differ between the 2 groups in the per-protocol analysis (57.1%; 95% CI, 38.8–71.9 vs 62.2%; 95% CI, 49.0–72.9; $P = .475$) (Supplementary Figure 8).

A post hoc analysis was performed according to the percentile distribution of daily energy intake (total kcal and kcal/kg/BW) (<33rd, 33rd–66th, and >66th percentile). This analysis involved 93% of the total population and only included patients for whom daily calorie intake information was available (Supplementary Figure 9). Regardless of the allocated therapy, patients with a daily calorie intake less than 21.5 kcal/kg/day (<33rd percentile) had a significantly higher cumulative risk of 6-month mortality than those with a daily calorie intake of 21.5 kcal/kg/day or more (65.8%; 95% CI, 48.8–78.4 vs 33.1%; 95% CI, 23.1–43.4; $P < .0001$) (Figure 2*A*). Similarly, patients with an energy intake less than 1692 kcal/day (<33rd percentile) had a significantly higher cumulative risk of 6-month mortality than those with a daily energy intake of 1692 kcal/day or more (58.5%; 95% CI, 41.7–72.1 vs 36.8%; 95% CI, 26.4–47.2; $P = .0040$) (Figure 2*B*). Baseline characteristics were not significantly different between patients with a low daily calorie intake compared with the others (Supplementary Tables 1 and 2). In univariate analysis, in addition to a daily nutritional intake less than 21.5 kcal/kg/day (SHR, 3.01; 95% CI, 1.75–5.16; $P = .0001$), 9 other variables were associated significantly with an increased risk of 6-month mortality. In the multivariable analysis, low daily calorie intake (SHR, 3.08; 95% CI, 1.70–5.59; $P = .0002$), platelet count, serum sodium level, presence of encephalopathy, and MELD score were identified as independent prognostic factors associated with 6-month mortality (Table 3). When assessed by category of nutrient (ie, carbohydrate, protein, or lipid), all classes showed coherent effect size direction, indicating a deleterious effect of low daily dietary intake (Supplementary Table 3). In addition, patients with a daily calorie intake less than 21.5 kcal/kg/day had a higher cumulative risk of infection ($P < .0001$) and a trend toward a higher cumulative risk of HRS ($P = .057$) compared with those with a daily calorie intake of 21.5 kcal/kg/day or more.

Additional subgroup analyses assessing the association between allocated therapies in each subgroup of daily nutritional intake for primary and secondary end points were performed.

Overall, there was neither a significant difference between intensive enteral and conventional nutrition in patients with a calorie intake less than 21.5 kcal/kg/day nor in those with an intake of 21.5 kcal/kg/day or higher for primary and secondary end points. Similarly, we observed no difference when daily calorie intake was assessed in kcal/day (Supplementary Figures 10–12).

Alcohol Relapse

Among the 136 patients included, 27.2% (37 of 136) died during hospitalization. Information about alcohol relapse also was missing for 6.6% (9 of 136), and 1 patient (0.7%) was transplanted after his hospitalization but before the end of the 6-month follow-up period. Therefore, alcohol relapse was assessed for 65.4% (89 of 136) of the study population. Among evaluable patients, 32.6% (29 of 89) relapsed. The proportion of patients who experienced a relapse was not statistically different between the intensive and the control arms (55.2% [16 of 29] vs 44.8% [13 of 29]; 95% $P = .499$).

Safety

Serious adverse events considered related to enteral nutrition were reported in 5 patients in the intensive arm (3 patients had aspiration pneumonia, 1 patient had decompensated diabetes, and 1 patient had a severe worsening of encephalopathy), and 2 additional serious adverse events that were considered unlikely to be related to enteral feeding were reported (upper gastrointestinal bleeding in 1 patient and worsening of encephalopathy in 1 patient). Aspiration pneumonia rapidly led to death in 1 patient. Premature enteral feeding tube withdrawal (before the 14 days of intensive enteral nutrition) was reported in 33 patients (48.5%). Among those, the median duration of the feeding tube was only 5 days (2.5–10 days). The main reasons cited for discontinuation were feeding tube

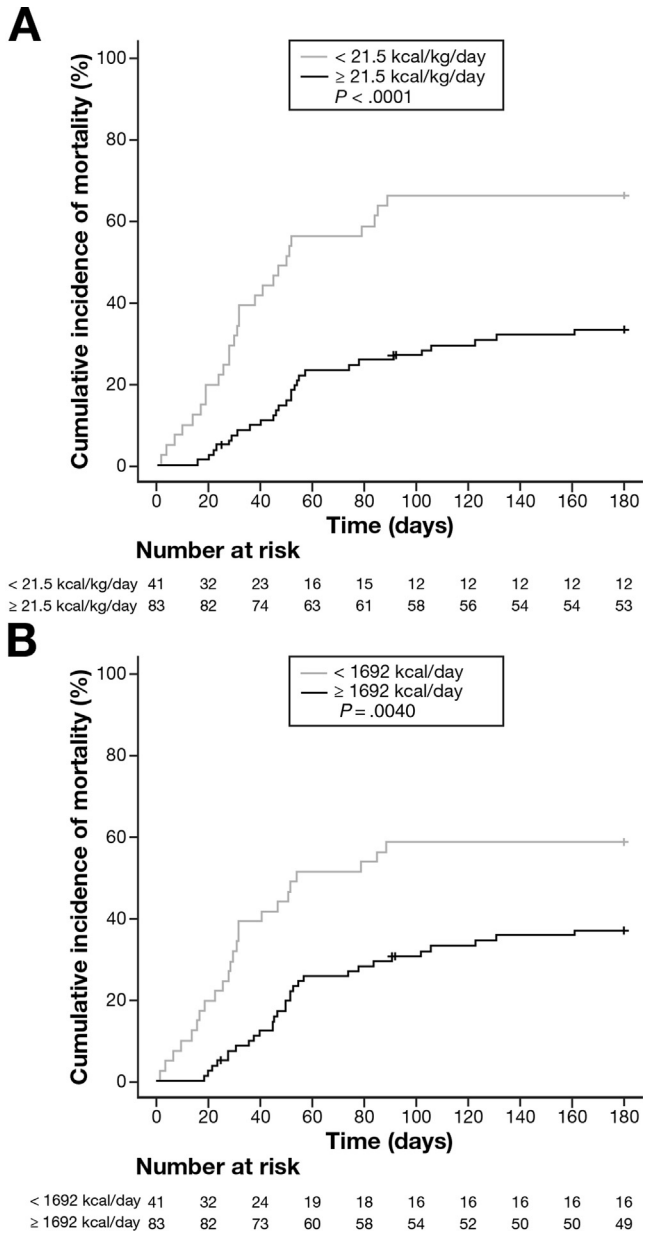

Figure 2. Cumulative incidence of 6-month mortality according to the distribution of daily calorie intake (total and per kg of body weight). (*A*) In the whole study population, regardless of allocated therapy, patients with a daily calorie intake less than 21.5 kcal/kg/BW/day (<33rd percentile) had a significantly higher cumulative risk of 6-month mortality than those with a daily calorie intake of 21.5 kcal/kg/day or greater (≥33rd percentile): 6-month survival (65.8%; 95% CI, 48.8–78.4 vs 33.1%; 95% CI, 23.1–43.4; $P < .0001$). (*B*) Similarly, patients with a total daily calorie intake less than 1692 kcal/day had a significantly higher cumulative risk of 6-month mortality than those with a daily calorie intake of 1692 kcal/day or more (58.5%; 95% CI, 41.7–72.1 vs 36.8%; 95% CI, 26.4–47.2; $P = .0040$).

intolerance in 15, noncompliance in 8, premature death in 1, aspiration pneumonia in 3, severe hyperglycemia in 1, hepatic encephalopathy in 3, and unknown cause in 2 cases. Four prognostic factors (ie, platelet and neutrophil count, serum sodium level, and MELD score) were identified as significantly associated with premature feeding tube withdrawal. However, in multivariable analysis, only serum sodium level remained independently associated (SHR, 0.94; 95% CI, 0.89–0.99; $P = .025$) (Supplementary Table 4).

Discussion

This randomized clinical trial in patients with biopsy-proven severe alcoholic hepatitis showed that the systematic administration of intensive enteral nutrition using a feeding tube in addition to corticosteroid treatment did not improve survival compared with conventional nutrition and corticosteroids.

In a previously published randomized trial, Cabre et al[13] reported that total enteral nutrition had comparable efficacy compared with corticosteroids in severe AH patients. Our study design differed from this previous study in that the duration of enteral nutrition was 14 days (compared with 28 days in the study by Cabre et al[13]), and patients in both arms received corticosteroids.

Interestingly, a post hoc analysis of the present study showed that, regardless of the allocated therapy, daily calorie intake was associated with 1- and 6-month mortality, independently of other prognostic factors, such as MELD and DF scores. Patients with a daily calorie intake less than 21.5 kcal/kg of body weight had a significantly higher risk of death and infections and showed a trend toward a higher incidence of HRS. Of note, these findings were not the consequence of more severe liver disease at baseline in patients with a low-calorie intake. Indeed, baseline characteristics were comparable between patients with a low daily calorie intake and those without. This daily calorie intake threshold is largely below the one recommended by the European Society for Clinical Nutrition and Metabolism (ie, 35 kcal/kg/BW).[11] The optimal energy requirements of critically ill patients remains under debate, and recent randomized controlled trials have highlighted that targeting full-replacement feeding in critical illness does not provide survival benefit.[26] Thus, these findings strongly suggest that a low daily calorie intake (<21.5 kcal/kg/BW) should be avoided in patients with severe AH.

In our study, tolerance of the feeding tube was an important issue because nearly half of the patients prematurely withdrew the enteral feeding tube (before the planned 14 days). Poor feeding tube tolerance in ALD patients has been reported previously in other trials.[13,27] Although the mean calorie intake was significantly higher in patients randomized to the intensive nutrition arm, the high rate of premature feeding tube withdrawal might have contributed to the lack of statistically significant difference in mortality between the groups. However, based on these study results, enteral nutrition using a feeding tube is not a benign intervention and cannot be recommended routinely in patients with severe AH. Therefore, the oral route should be preferred as the first-line intervention. However, in patients with insufficient daily energy intake (ie, <21.5 kcal/kg), the best route as well as the optimal duration to provide adequate nutritional intake remain unknown and require additional studies. Furthermore, these results may help in designing future trials because they

Table 3. Prognostic Factors of 6-Month Mortality in Univariate and Multivariable Analyses

	Univariate			Multivariable[a]		
	SHR	95% CI	*P*	SHR	95% CI	*P*
Intensive enteral nutrition, intervention vs control	0.81	0.50–1.32	.406			
Daily calorie intake, *kcal/kg/day*						
<21.5 (T1)	2.53	1.37–4.66	.0003			
21.5–29.9 (T2)	0.68	0.33–1.44				
≥29.9 (T3)	1.00					
Calorie intake, *kcal/kg/day*, <21.5 vs ≥21.5	3.01	1.75–5.16	.0001	3.08	1.70–5.59	.0002
Age, *y*	1.03	1.00–1.06	.096	-	-	-
Sex, men vs women	1.18	0.71–1.95	.531			
BMI, kg/m^2	0.99	0.95–1.03	.572			
INR	1.72	1.25–2.37	.0008	-	-	-
Platelets, /μL per increase of 1000	0.95	0.91–0.98	.003	0.92	0.87–0.96	.0004
Bilirubin level, *mg/dL*	1.03	1.00–1.06	.028	-	-	-
DF[b]	1.01	1.00–1.02	<.0001	0.99	0.97–1.00	.103
MELD[b]	1.14	1.08–1.22	<.0001	1.24	1.10–1.40	.0003
Serum creatinine level, *mg/dL*	3.94	1.52–10.21	.005	-	-	-
Serum sodium level, *mEq/L*	0.95	0.91–0.99	.019	0.93	0.89–0.97	.001
Albumin level, *g/dL*	0.99	0.94–1.04	.642			
AST level, *IU/L*	1.00	0.99–1.01	.278			
Leukocytes, /μL per increase of 10,000	0.74	0.39–1.43	.372			
Neutrophils, /μL per increase of 10,000	0.70	0.33–1.48	.348			
Lille score[b]	6.43	2.39–17.25	.0002	1.88	0.63–5.63	.260
Ascites, presence vs absence	1.10	0.66–1.85	.717			
Encephalopathy, presence vs absence	1.66	1.01–2.74	.046	1.85	1.00–3.42	.049

AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease; T, tertile.
[a]Variables with a significance level of less than 0.10 in univariate analyses were included in the multivariable Fine and Gray[21] regression model.
[b]To avoid bias related to the effect of colinearity, when composite scores (Lille, DF, and MELD) were tested, factors included in them were not included in the multivariable analysis comprising these scores.

provide a better idea of the minimum daily nutritional intake that should be targeted in this population.

This study should be interpreted in light of a number of limitations. The hypothesis regarding the reduction of mortality (primary end point) was probably too optimistic (ie, a decrease in 6-month mortality rate from 50% to 25%). A 10% decrease in mortality rate probably would have been more realistic and still of great clinical interest. Nevertheless, this would have required recruiting more than 400 patients per arm. Moreover, this study was powered for the primary end point but conversely probably was underpowered to detect a difference in secondary end points (eg, incidence of infections and HRS at 6 months). Another limitation of the present study was the lack of specific pretreatment assessment of nutritional state, apart from BMI and albumin serum level. However, assessment of nutritional status in patients with alcoholic liver disease is quite difficult and challenging. The majority of the available tests can be influenced by the underlying liver disease or by factors such as ascites or alcohol consumption.[28] Finally, the percentage of screening failures was low compared with the most recent and largest randomized controlled trial to date,[7] and it cannot be excluded that some screening failures were not reported in the present study. However, this proportion is in line with other recently published randomized controlled trials.[29,30] The results regarding 6-month mortality are somewhat disappointing because 47.8% of the patients were dead after 6 months of follow-up evaluation. This 6-month mortality incidence is higher than previously reported in some recent studies including in patients with severe AH treated with corticosteroids or pentoxifylline.[7,29] One potential explanation could be the participation of both expert and nonexpert centers in the management of severe AH patients. However, no center effect was observed and very similar mortality rates were reported in centers with strong experience in clinical trials including AH patients. On the other hand, this approach reflects daily clinical practice in the closest possible way and the reported mortality rate is similar to a previous observational study performed in Belgium.[24]

In conclusion, systematic intensive enteral nutrition using a feeding tube in corticosteroid-treated severe AH patients did not increase survival. However, low energy intake was associated with an increased risk of mortality and bacterial infections. These findings strongly suggest that early identification of insufficient energy intake and adequate nutritional support should be targeted in this population with a deleterious short-term prognosis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.12.038.

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Conflicts of interest
The authors disclose no conflicts.

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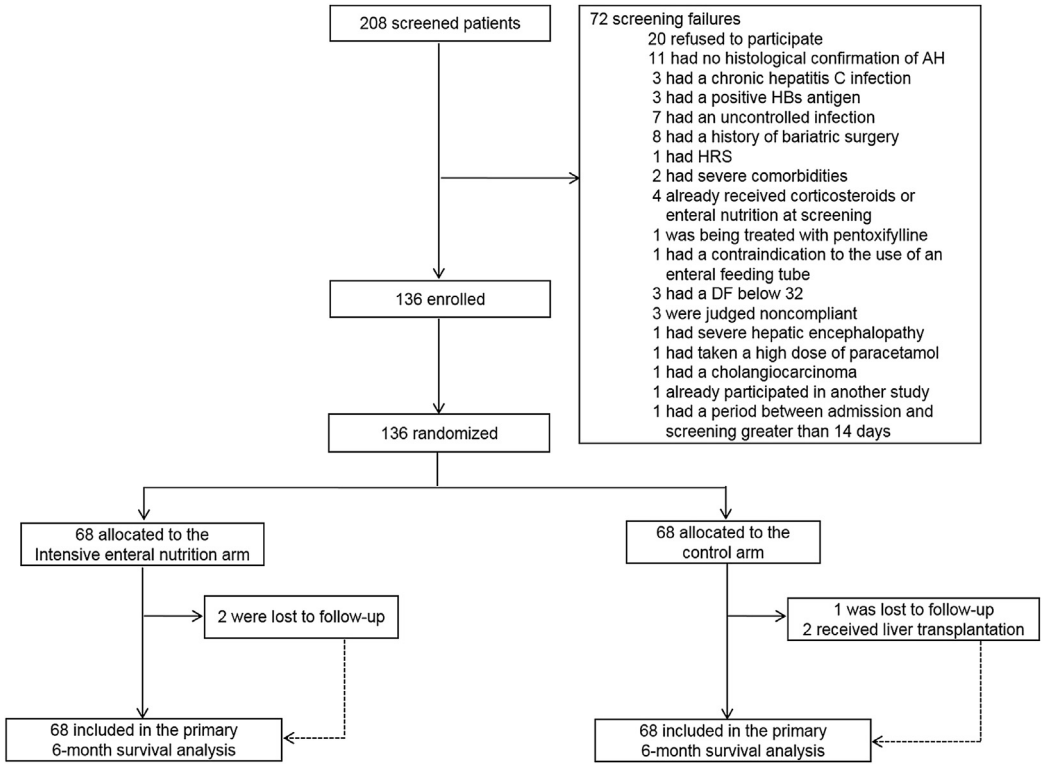
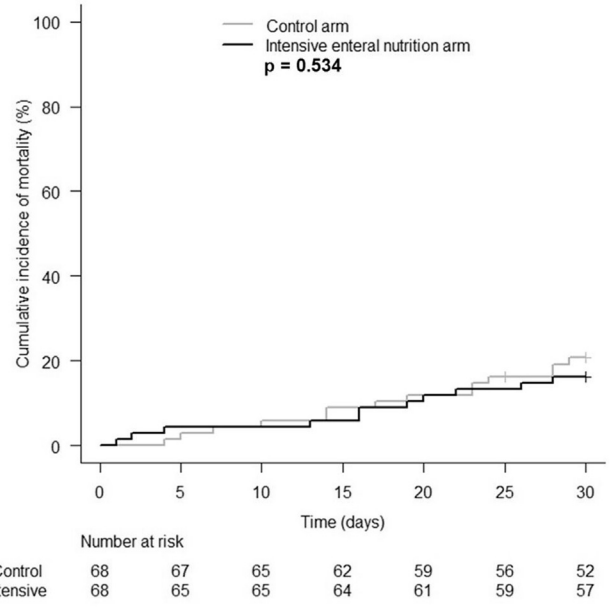
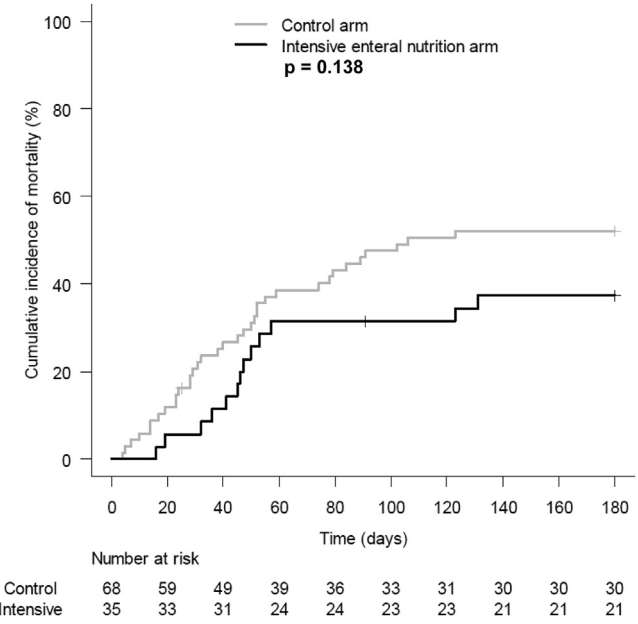


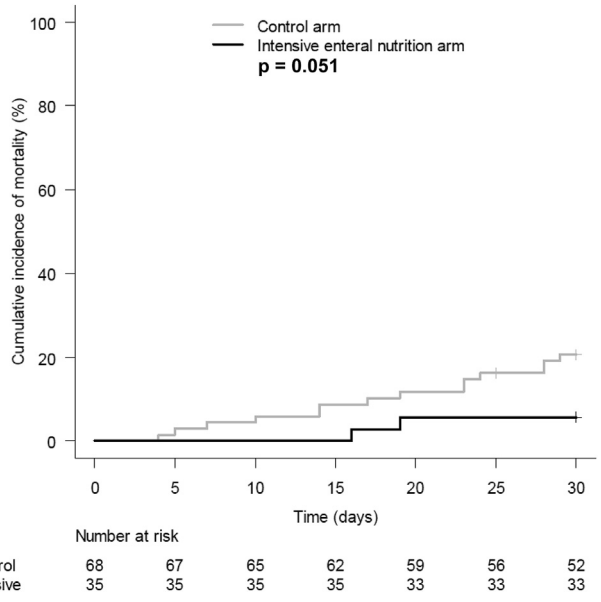
Supplementary Figure 1. Patient disposition.



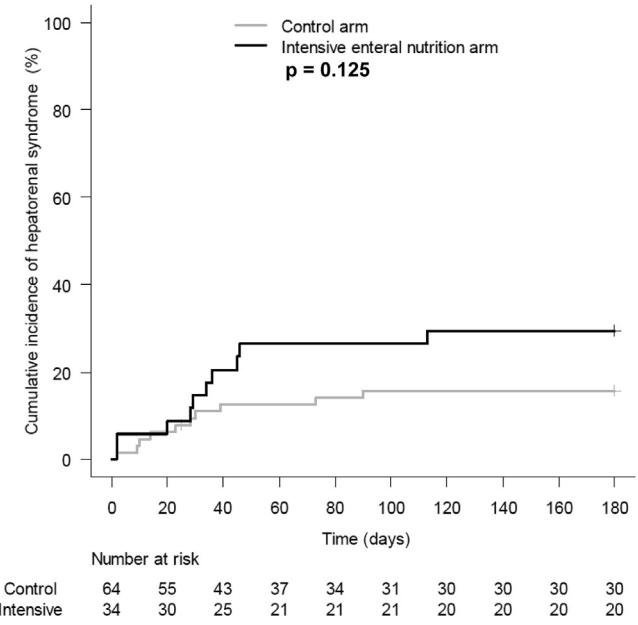
Supplementary Figure 2. Cumulative incidence of 1-month mortality according to the intervention group. There was no significant difference in the cumulative risk of mortality at 1 month between the intensive and the control arms in the intention-to-treat analysis (16.2%; 95% CI, 8.6–25.9 in the intensive arm vs 20.7%; 95% CI, 11.9–31.1 in the control arm; $P = .534$).



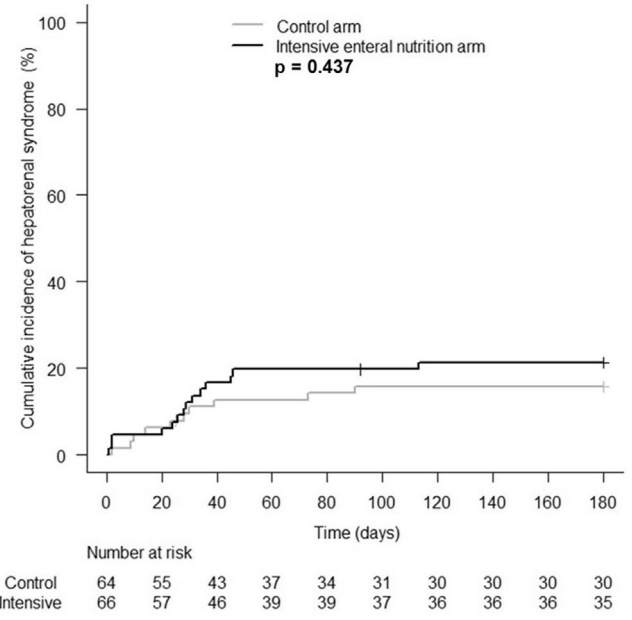
Supplementary Figure 3. Cumulative incidence of 6-month mortality according to the intervention group in the per-protocol population. There was no significant difference in the cumulative risk of mortality at 6 months between the intensive and the control arms in the per-protocol population (37.4%; 95% CI, 21.5–53.3 in the intensive arm vs 52.1%; 95% CI, 39.4–63.4 in the control arm; $P = .138$).



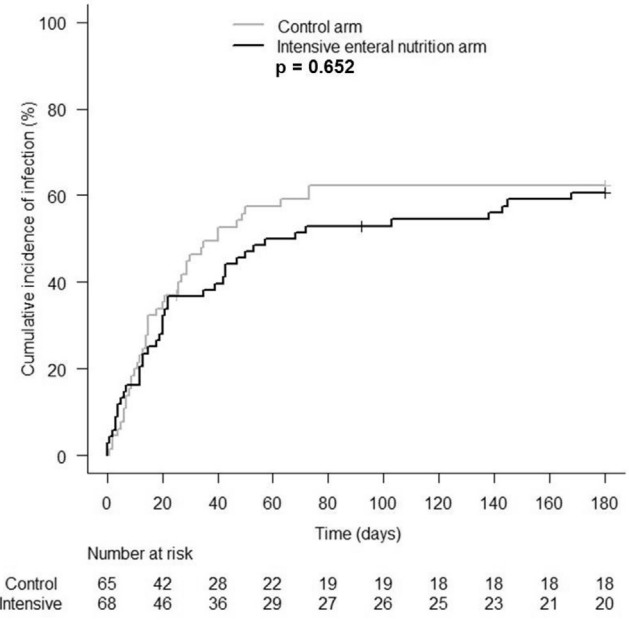
Supplementary Figure 4. Cumulative incidence of 1-month mortality according to the intervention group in the per-protocol population. There was no significant difference in the cumulative risk of mortality at 6 months between the intensive and the control arms in the per-protocol population (5.7%; 95% CI, 1.0–16.9 vs 20.7%; 95% CI, 11.9–31.0; $P = .051$).



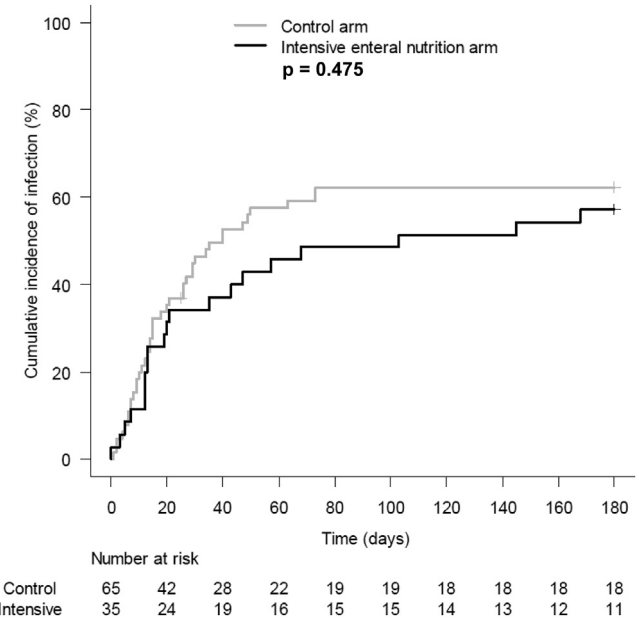
Supplementary Figure 6. Cumulative incidence of hepatorenal syndrome at 6 months according to the intervention group in the per-protocol population. There was no significant difference in the cumulative incidence of hepatorenal syndrome during the 6-month study period between the intensive arm compared with the control arm in the per-protocol analysis (29.4%; 95% CI, 15.1–45.2 vs 15.8%; 95% CI, 8.0–25.9; $P = .125$).



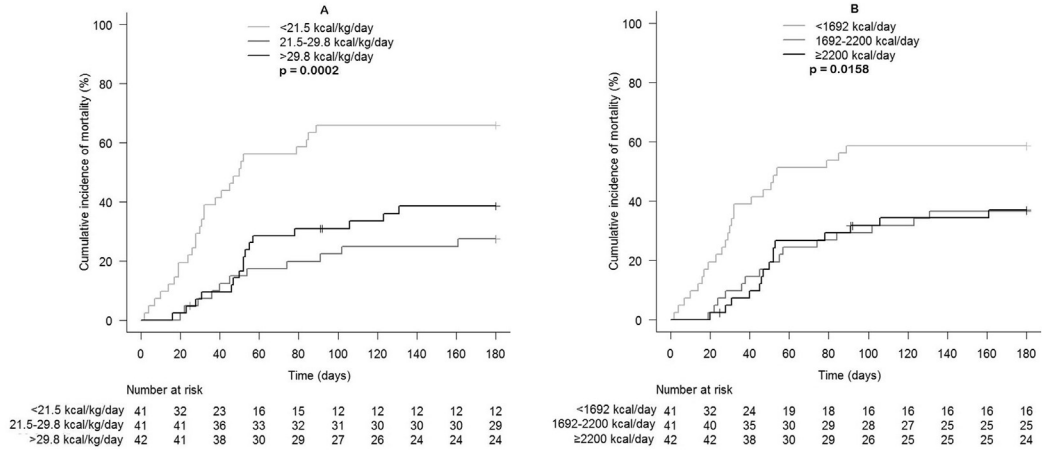
Supplementary Figure 5. Cumulative incidence of hepatorenal syndrome at 6 months according to the intervention group. There was no significant difference in the cumulative incidence of hepatorenal syndrome during the 6-month study period between the intensive arm compared with the control arm in the intention-to-treat analysis (21.3%; 95% CI, 12.3–31.9 vs 15.8%; 95% CI, 8.0–25.9; $P = .437$).



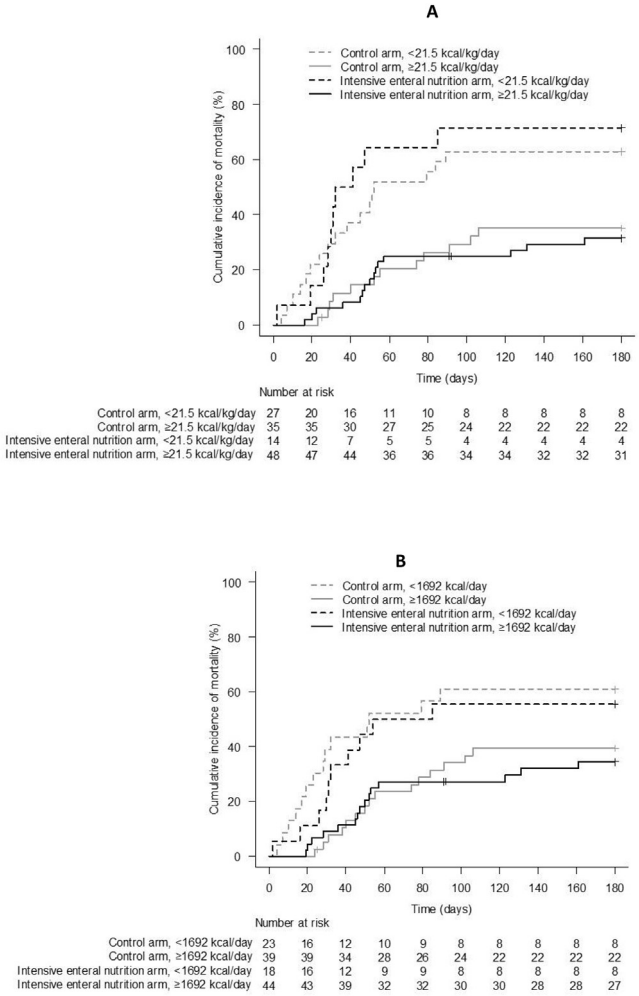
Supplementary Figure 7. Cumulative incidence of infection at 6 months according to the intervention group. There was no significant difference of the cumulative incidence of infection during the 6-month study period between the intensive compared with the control arm in the intention-to-treat analysis (60.6%; 95% CI, 47.7–71.2 vs 62.2%; 95% CI, 49.0–72.9; $P = .652$).



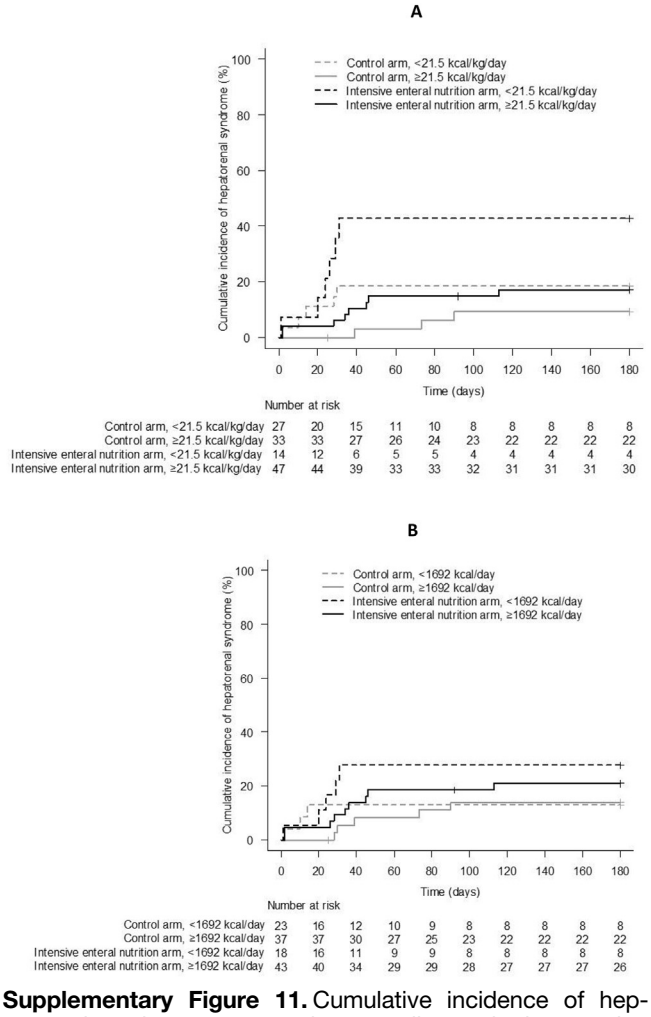
Supplementary Figure 8. Cumulative incidence of infection at 6 months according to the intervention group in the per-protocol population. There was no significant difference of cumulative incidence of infection during the 6-month study period between the intensive compared with the control arm in the per-protocol analysis (57.1%; 95% CI, 38.8–71.9 vs 62.2%; 95% CI, 49.0–72.9; $P = .475$).



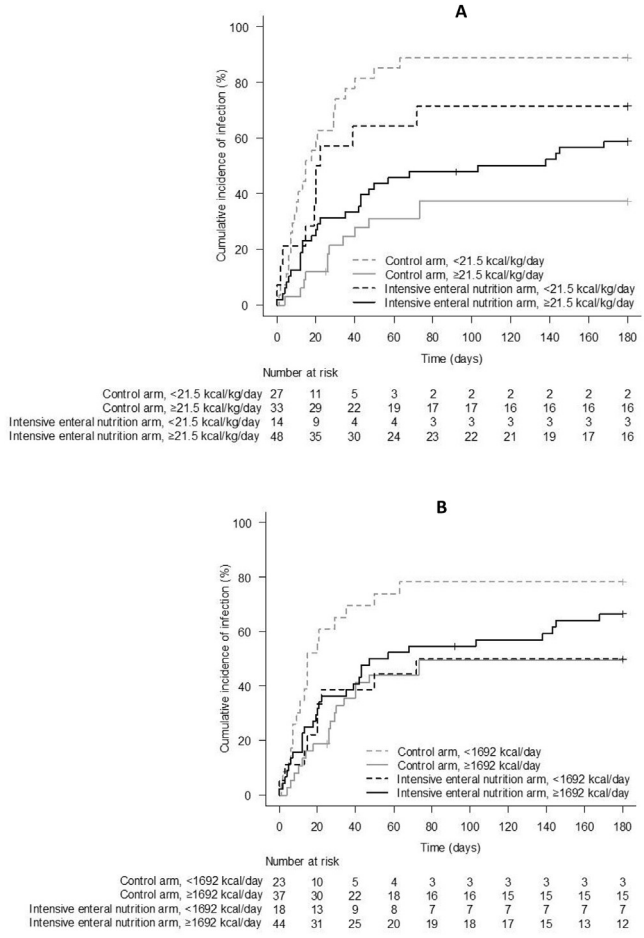
Supplementary Figure 9. Cumulative incidence of mortality according to the distribution of daily calorie intake (total and per kg of body weight). In the whole study population, regardless of allocated therapy, the cumulative incidence of mortality differed significantly (65.8%; 95% CI, [48.8–78.4]; 27.4%; 95% CI, [14.6–41.8]; 38.6%; 95% CI, [23.8–53.2]; $P = .0002$) according to the distribution of daily calorie intake per kg of body divided into tertiles ($<$21.5 kcal/kg/day, 21.5–29.8 kcal/kg/day, and $>$29.8 kcal/kg/day, respectively). Similarly, the cumulative incidence of mortality differed significantly (58.8%; 95% CI, [41.7–72.1]; 36.6%; 95% CI, [22.1–51.2]; 36.9%; 95% CI, [22.2–51.7]; $P = .0158$) according to the distribution of total daily calorie intake divided into tertiles ($<$1692 kcal/day, 1692–2200 kcal/day, and $\geq$2200 kcal/day, respectively).



Supplementary Figure 10. Cumulative incidence of 6-month mortality according to the intervention group and the distribution of daily calorie intake. (*A*) In the whole study population, the cumulative risk of 6-month mortality was neither significantly different between the intensive and control arms in patients with a daily calorie intake less than 21.5 kcal/kg/day (71.4%; 95% CI, 37.6–89.1 vs 63.0%; 95% CI, 41.3–78.5; $P = 1.000$), nor in those with a daily calorie intake of 21.5 kcal/kg/day or greater (31.6%; 95% CI, 18.9–45.1 vs 35.2%; 95% CI, 19.6–51.3; $P = 1.000$). (*B*) Similarly, when daily calorie intake was assessed in kcal/day there was neither a difference in cumulative incidence of 6-month mortality between patients allocated to the intensive arm and those allocated to the control arm in patients with a daily calorie intake less than 1692 kcal/day (55.6%; 95% CI, 29.3–75.4 vs 60.9%; 95% CI, 37.3–77.9; $P = 1.000$), nor in those with a daily calorie intake of 1692 kcal/day or greater (34.5%; 95% CI, 20.7–48.8 vs 39.4%; 95% CI, 23.9–54.6; $P = 1.000$).



Supplementary Figure 11. Cumulative incidence of hepatorenal syndrome at 6 months according to the intervention group and the distribution of daily calorie intake. (*A*) In the whole study population, there was neither a significant difference in the cumulative incidence of hepatorenal syndrome during the 6-month study period between the intensive and control arms in patients with a daily calorie intake less than 21.5 kcal/kg/day (42.9%; 95% CI, 16.5–67.2 vs 18.5%; 95% CI, 6.5–35.2; $P = .670$), nor in those with a daily calorie intake of 21.5 kcal/kg/day or greater (17.1%; 95% CI, 7.9–29.2 vs 9.4%; 95% CI, 2.3–22.6; $P = 1.000$). (*B*) Similarly, when daily calorie intake was assessed in kcal/day there was neither a difference in the cumulative incidence of hepatorenal syndrome during the 6-month study period between patients allocated to the intensive arm and those allocated to the control arm in patients with a daily calorie intake less than 1692 kcal/day (27.8%; 95% CI, 9.6–49.6 vs 13.0%; 95% CI, 3.1–30.2; $P = 1.000$), nor in those with a daily calorie intake of 1692 kcal/day or greater (21.0%; 95% CI, 10.3–34.3 vs 27.8%; 95% CI, 9.6–49.6; $P = 1.000$).



Supplementary Figure 12. Cumulative incidence of infection at 6 months according to the intervention group and the distribution of daily calorie intake. (*A*) In the whole study population, there was neither a significant difference in the cumulative incidence of infections during the 6-month study period between the intensive and control arms in patients with a daily calorie intake less than 21.5 kcal/kg/day (71.4%; 95% CI, 37.1–89.2 vs 88.9%; 95% CI, 66.0–96.7; $P = 1.000$), nor in those with a daily calorie intake of 21.5 kcal/kg/day or greater (58.8%; 95% CI, 43.2–71.5 vs 37.3%; 95% CI, 20.8–53.8; $P = .404$). (*B*) Similarly, when daily calorie intake was assessed in kcal/day there was neither a difference in the cumulative incidence of infections during the 6-month study period between patients allocated to the intensive arm and those allocated to the control arm in patients with a daily calorie intake less than 1692 kcal/day (50.0%; 95% CI, 24.8–70.8 vs 78.3%; 95% CI, 53.1–91.0; $P = .285$), nor in those with a daily calorie intake of 1692 kcal/day or greater (66.5%; 95% CI, 49.9–78.7 vs 49.7%; 95% CI, 32.3–64.8; $P = 1.000$).

Supplementary Table 1. Baseline Characteristics of Patients According to Daily Calorie Intake (kcal/kg) During 14 Days

Characteristics	<21.5 kcal/kg/day (n = 41)	Missing data, n (%)	≥21.5 kcal/kg/day (n = 83)	Missing data, n (%)	*P*
Intensive enteral nutrition, n (%)	14 (34.2)	0	48 (57.8)	0	.013
Age, *y*	52.5 ± 9.3	0	49.5 ± 8.2	0	.075
Male sex, n (%)	28 (68.3)	0	50 (60.2)	0	.383
BMI, kg/m^2	29.9 ± 6.7	2	25.8 ± 5.3	4	.0005
Ascites, presence vs absence, n (%)	30 (73.2)	0	56 (67.5)	0	.517
Ascites, n (%)		0		0	
Grades 0–1	11 (26.8)		31 (37.4)		.128[a]
Grade 2	18 (43.9)		40 (48.2)		
Grade 3	12 (29.3)		12 (14.4)		
Encephalopathy, presence vs absence, n (%)	15 (36.6)	0	26 (31.7)	1	.589
Encephalopathy, n (%)		0		1	
Grade 0	26 (63.4)		56 (68.3)		.178
Grade I	5 (12.2)		16 (19.5)		
Grades II–III	10 (24.4)		10 (12.2)		
INR	1.8 (1.6–2.2)	0	1.8 (1.6–2.0)	0	.376
Platelets, $\times 10^3/\mu L$	95,000 (75,500–158,500)	1	120,000 (77,000–199,000)	0	.206
Bilirubin level, *mg/dL*	13.0 (7.5–19.9)	0	12.4 (7.8–22.5)	0	.882
Creatinine level, *mg/dL*	0.8 (0.6–1.0)	0	0.7 (0.5–0.9)	0	.175
Albumin level, *g/L*	25 (23–30)	0	25 (23–28)	7	.904
Sodium level, *mEq/L*	134 (131–138)	0	135 (132–138)	1	.709
AST level, *IU/L*	112 (86–162)	0	122 (86–167)	0	.758
Leukocyte level, $/\mu L$	8935 (6100–10,650)	1	8780 (6750–11,600)	1	.445
Neutrophil level, $/\mu L$	5660 (4200–7500)	3	6020 (4300–8870)	3	.429
MELD	23.7 (20.4–25.6)	0	22.2 (20.5–24.8)	0	.432
DF	55.9 (40.1–70.0)	0	50.5 (40.5–64.2)	0	.369

NOTE. Variables with a normal distribution are presented as means ± SD. Skewed variables are presented as median (interquartile range).
AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease.
[a]When comparing patients with grade 3 ascites between the 2 groups, the *P* value was .050.

Supplementary Table 2. Baseline Characteristics of Patients According to Daily Calorie Intake (kcal) During 14 Days

Characteristics	<1692 kcal/day (n = 41)	Missing data, n (%)	≥ 1692 kcal/day (n = 83)	Missing data, n (%)	*P*
Intensive enteral nutrition, n (%)	18 (43.9)	0	44 (53.0)	0	.340
Age, *y*	52.3 ± 8.8	0	49.6 ± 8.5	0	.099
Male sex, n (%)	22 (53.7)	0	56 (67.5)	0	.134
BMI, kg/m^2	25.9 ± 6.3	2	27.7 ± 5.9	4	.127
Ascites, presence vs absence, n (%)	32 (78.1)	0	54 (65.1)	0	.140
Ascites, n (%)		0		0	
Grades 0–1	10 (24.4)		32 (38.6)		.292
Grade 2	22 (53.7)		36 (43.4)		
Grade 3	9 (21.9)		15 (18.0)		
Encephalopathy, presence vs absence, n (%)	18 (43.9)	0	23 (28.1)	1	.079
Encephalopathy, n (%)		0		1	
Grade 0	23 (56.1)		59 (72.0)		.154
Grade I	8 (19.5)		13 (15.9)		
Grades II–III	10 (24.4)		10 (12.2)		
INR	1.7 (1.6–2.2)	0	1.8 (1.6–2.0)	0	.772
Platelets, $\times 10^3/\mu L$	123,000 (76,500–210,500)	0	111,500 (72,500–176,750)	1	.697
Bilirubin level, *mg/dL*	12.4 (7.7–20.5)	0	13.0 (7.7–22.3)	0	.610
Creatinine level, *mg/dL*	0.8 (0.6–1.0)	0	0.7 (0.6–0.9)	0	.306
Albumin level, *g/L*	25 (21–29)	1	26 (23–29)	6	.501
Sodium level, *mEq/L*	134 (130–138)	0	135 (132–138)	1	.385
AST level, *IU/L*	112 (81–163)	0	119 (87–167)	0	.684
Leukocyte level, $/\mu L$	9000 (6650–11,150)	1	8240 (6230–11,300)	2	.466
Neutrophil level, $/\mu L$	6200 (4800–7890)	2	5560 (3684–8630)	6	.447
MELD	23.3 (20.2–25.1)	0	22.2 (20.5–25.2)	0	.614
DF	53.7 (39.5–71.5)	0	51.2 (40.5–68.1)	0	.873

NOTE. Variables with a normal distribution are presented as means ± SD. Skewed variables are presented as median (interquartile range).
AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease.

Supplementary Table 3. Association Between 6-Month Mortality and Daily Intake of Proteins, Carbohydrates, and Lipids

	Univariate		
	SHR	95% CI	*P*
Proteins, *g/day* (n = 113)			.075[a]
T1 (<77.6)	1.78	0.92–3.44	
T2 (77.6–104)	0.85	0.43–1.67	
T3 (>104)	1.00		
T1 vs (T2 + T3)	1.93	1.08–3.42	.026
Carbohydrates, *g/day* (n = 102)			.193[a]
T1 (<198.5)	1.86	0.95–3.67	
T2 (198.5–255)	1.27	0.63–2.54	
T3 (>255)	1.00		
T1 vs (T2 + T3)	1.66	0.92–3.00	.094
Lipids, *g/day* (n = 102)			.007[a]
T1 (<65)	3.11	1.51–6.40	
T2 (65–86.2)	1.59	0.77–3.30	
T3 (>86.2)	1.00		
T1 vs (T2 + T3)	2.42	1.34–4.36	.003

T, tertile 1.
[a]*P* value for the association between a class of nutrients divided into tertiles.

Supplementary Table 4. Prognostic Factors of Premature Withdrawal in Univariate and Multivariable Analyses

	Univariate			Multivariable[a]		
	SHR	95% CI	*P*	SHR	95% CI	*P*
Age, *y*	1.00	0.97–1.04	.886			
Sex, men vs women	1.24	0.56–2.76	.591			
BMI, kg/m^2	1.04	0.99–1.10	.124			
INR	0.55	0.22–1.43	.223			
Platelet count, /μL per increase of 1000	1.03	1.00–1.06	.040	1.01	0.96–1.06	.603
Bilirubin level, *mg/dL*	0.98	0.94–1.03	.522			
DF	0.98	0.97–1.00	.119			
MELD[b]	0.91	0.83–1.01	.088	0.94	0.84–1.04	.224
Creatinine level, *mg/dL*	1.16	0.31–4.34	.828			
Sodium level, *mEq/L*	0.93	0.88–0.98	.008	0.94	0.89–0.99	.025
Albumin level, *g/L*	0.99	0.92–1.07	.877			
AST level, *IU/L*	1.00	1.00–1.01	.636			
Leukocyte count, /μL per increase of 10,000	1.36	0.55–3.35	.508			
Neutrophil count, /μL per increase of 10,000	2.09	0.90–4.86	.087	1.44	0.42–4.92	.529
Lille score[b]	0.87	0.21–3.70	.854			
Ascites, presence vs absence	1.34	0.55–3.28	.521			
Ascites						
Grades 0–1	1.00		.512			
Grade 2	1.50	0.58–3.89				
Grade 3	1.79	0.67–4.78				
Encephalopathy, presence vs absence	1.17	0.57–2.44	.666			
Encephalopathy						
Grade 0	1.00					
Grade I	1.40	0.64–3.10	.655			
Grades II–III	0.89	0.27–2.88				

AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease.
[a]Variables with a significance level of less than 0.10 in univariate analyses were included in the multivariable Fine and Gray[21] regression model.
[b]To avoid bias related to the effect of colinearity, when composite scores (Lille, DF, and MELD) were tested, factors included in them were not included in the multivariable analysis comprising these scores.