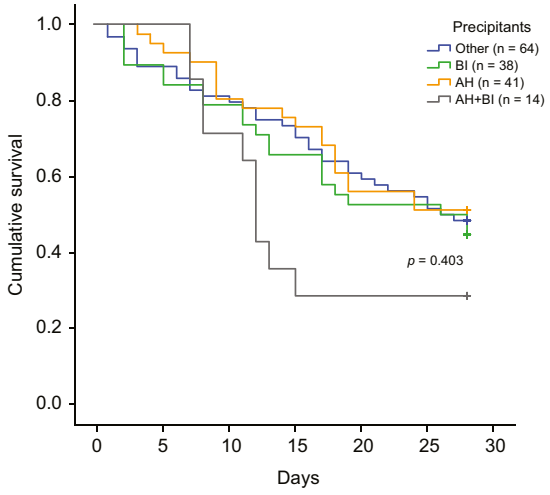
Defining the prognosis of critically ill patients with alcohol-related liver disease

To the Editor:

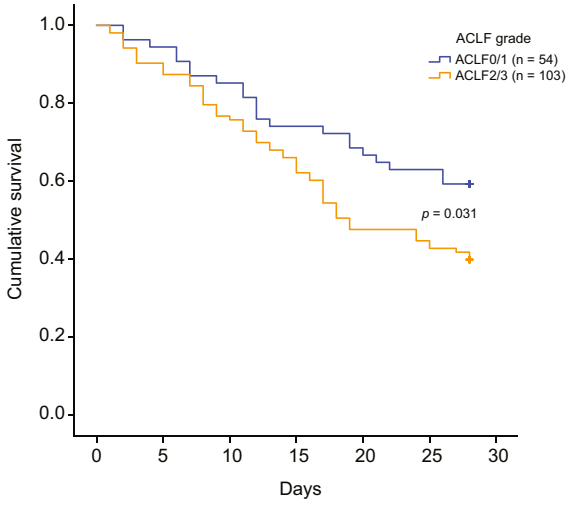
We read with great interest the results of the PREDICT study, which identified that the most common precipitants (>96% of cases) of acute decompensation (AD) were bacterial infection (BI) and alcoholic hepatitis (AH), either alone or in combination with other precipitating events (PEs).[1] Moreover, short-term outcomes, including development of ACLF and 90-day mortality, were related to number of PEs but independent of the type of PE. This important study suggests the importance of targeted strategies to manage organ failure rather than type of PE. However, the greatest resource utilization and poorest outcomes are in critically ill cirrhotic patients in whom the contribution of PEs to outcome has not been specifically studied.

Herein, we present data from a prospectively maintained database of consecutive cirrhotic patients admitted to the Royal Free intensive care unit (ICU) 2010-2015. Details of this cohort have been previously described.[2] Only patients with cirrhosis related to alcohol were included for this analysis. Exclusion criteria were: hepatocellular or other cancer, major intra- or extra-hepatic surgery, and patients transferred only for transjugular intrahepatic portosystemic shunt implantation. The primary endpoint of the analysis was 28-day mortality. BI was defined as culture-positive blood, urine or ascites, or ascitic fluid polymorphonuclear leukocytes >250/μl. AH was defined according to NIAAA criteria. Acute-on-chronic liver failure (ACLF) was defined according to EASL-CLIF criteria. Student's *t* test, Mann-Whitney *U* test, ANOVA or Chi-squared test were used depending on type and distribution of the data. Cox proportional-hazards model was used to estimate risk of 28-day survival.

After inclusions and exclusions were applied, 157 patients were included. The reasons for ICU admission were: AH (41, 29.9%), BI (38, 24.2%), AH+BI (14, 8.9%), and others (64, 43.3%) including variceal haemorrhage (VH, n = 30), non-VH bleeding



Number at risk:							
BI	38	34	30	25	20	20	19
AH	41	39	33	31	23	21	21
BI + AH	14	14	10	5	4	4	4
Others	64	57	52	47	39	35	31



Number at risk:							
ACLF grade 0/1	54	51	46	40	37	34	32
ACLF grade 2/3	103	93	76	68	49	46	43

Fig. 1. 28-day survival according to precipitating event or ACLF grade. Left panel: Kaplan-Meier of 28-day survival stratified according to type of precipitating event; no significant difference was found between groups (Log-rank test, $p = 0.403$). Right panel: Kaplan-Meier of 28-day survival stratified according to ACLF grade; mortality was significantly greater in ACLF grade 2/3 than ACLF grade 0/1 (Log-rank test, $p = 0.031$). ACLF, acute-on-chronic liver failure.

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(n = 2), post-operative (n = 4) and viral hepatitis (n = 2). ACLF was present in 127 patients (80.9%) and non-ACLF AD in 30 (19.1%). Most patients had ACLF grade 2/3 (103 [65.6%]).

At day 28, 84 patients (53.5%) were dead or transplanted (n = 1) (non-survivor group), and 73 (46.5%) survived (survivor group). There were no differences in PE between non-survivors and survivors (p = 0.509). Survival rate was 51.2% in AH, 44.7% in BI, 28.6% in AH+BI and 48.4% in others. Although AH+BI showed a trend to higher 28-day mortality, no significant difference between groups was found (p = 0.403, Fig. 1 left panel). Mortality was significantly higher in ACLF grade 2/3 *vs.* ACLF 0/1 (73.8% *vs.* 56.2%, p = 0.031, Fig. 1 right panel). Disease prognostic scores were examined for 28-day mortality. On multivariate analysis, only CLIF-C-ACLF score >56 independently predicted 28-day mortality (hazard ratio 1.950; 95% CI 1.176–3.234; p = 0.010). CLIF-C-ACLF score had the highest AUROC (0.68) compared to Maddrey (0.60) or model for end-stage liver disease-sodium (0.59).

These data support the findings of the PREDICT study and suggest that the grade of ACLF determines outcome in this population rather than the presence of AH or other PEs. The overarching implication is that organ failure-based prognostic models may be better than disease-specific scores to risk stratify patients with alcohol-related liver disease presenting with AD.

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Conflict of interest
RJ has research collaborations with Takeda and Yaqrit, consults for Mallinckrodt and Yaqrit and has received speaking fees from Grifols. RJ is the founder of Yaqrit Limited and Thoeris GmBh, which is developing UCL inventions for treatment of patients with cirrhosis.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
SL, RJ and GM conceived the study. SL, BA and RK contributed to data collection. SL and GM contributed to data analysis. All authors contributed to drafting and reviewing the manuscript.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.04.054.

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Are the different MAFLD subtypes based on the inclusion criteria correlated with all-cause mortality?

To the Editor:
Metabolic dysfunction-associated fatty liver disease (MAFLD) is a newly proposed diagnosis which has attracted substantial attention.[1,2] MAFLD, which is different from the previous term non-alcoholic fatty liver disease (NAFLD), is defined by its own set of inclusion criteria rather than exclusion criteria. MAFLD is diagnosed in patients who have both hepatic steatosis and metabolic risk factors.[1,3–5] As we know, MAFLD has substantial heterogeneity and MAFLD may be categorized into different subtypes.[1,6] However, no studies have examined the outcome of MAFLD subtypes based on the inclusion criteria.

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Therefore, we analyzed adults from NHANES III (1988-1994). All participants underwent a passive mortality follow-up through December 31, 2015. We excluded individuals who were pregnant or had missing data on hepatic ultrasound, follow-up time, BMI, waist circumference, fasting glucose, serum cholesterol, alanine aminotransferase and glycated hemoglobin. In total, 12,377 individuals were included in the analysis. According to the ultrasound examination, 4,550 participants had hepatic steatosis. Firstly, 846 individuals who had glycosylated hemoglobin ≥6.5% or fasting glucose ≥126 mg/dl or a history of diabetes were categorized as MAFLD (diabetes subtype). And then in individuals without diabetes, 2,637 participants with BMI ≥25 were treated as having MAFLD (overweight/obesity subtype). Finally, 402 lean individuals who had 2 metabolic risk abnormalities among the non-diabetic population