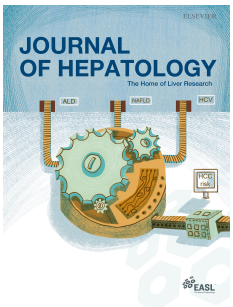
Journal Pre-proof



Determinants of mortality in patients with cirrhosis and uncontrolled variceal bleeding

Rahul Kumar, Annarein J.C. Kerbert, M. Faisal Sheikh, Noam Roth, Joana A.F. Calvao, Monica D. Mesquita, Ana I. Barreira, Haqeeqat S. Gurm, Komal Ramsahye, Rajeshwar P. Mookerjee, Dominic Yu, Neil H. Davies, Gautam Mehta, Banwari Agarwal, David Patch, Rajiv Jalan

PII: S0168-8278(20)30381-0

DOI: https://doi.org/10.1016/j.jhep.2020.06.010

Reference: JHEPAT 7805

To appear in: *Journal of Hepatology*

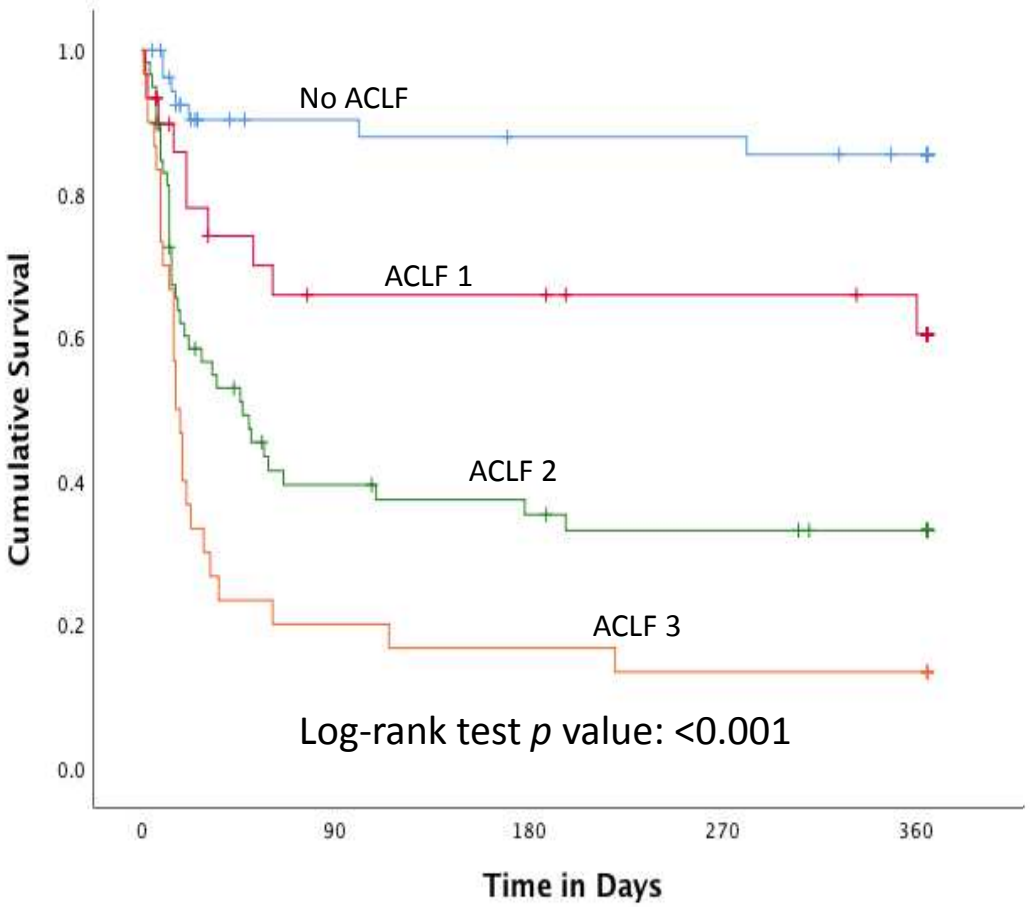
Received Date: 16 February 2020

Revised Date: 4 June 2020

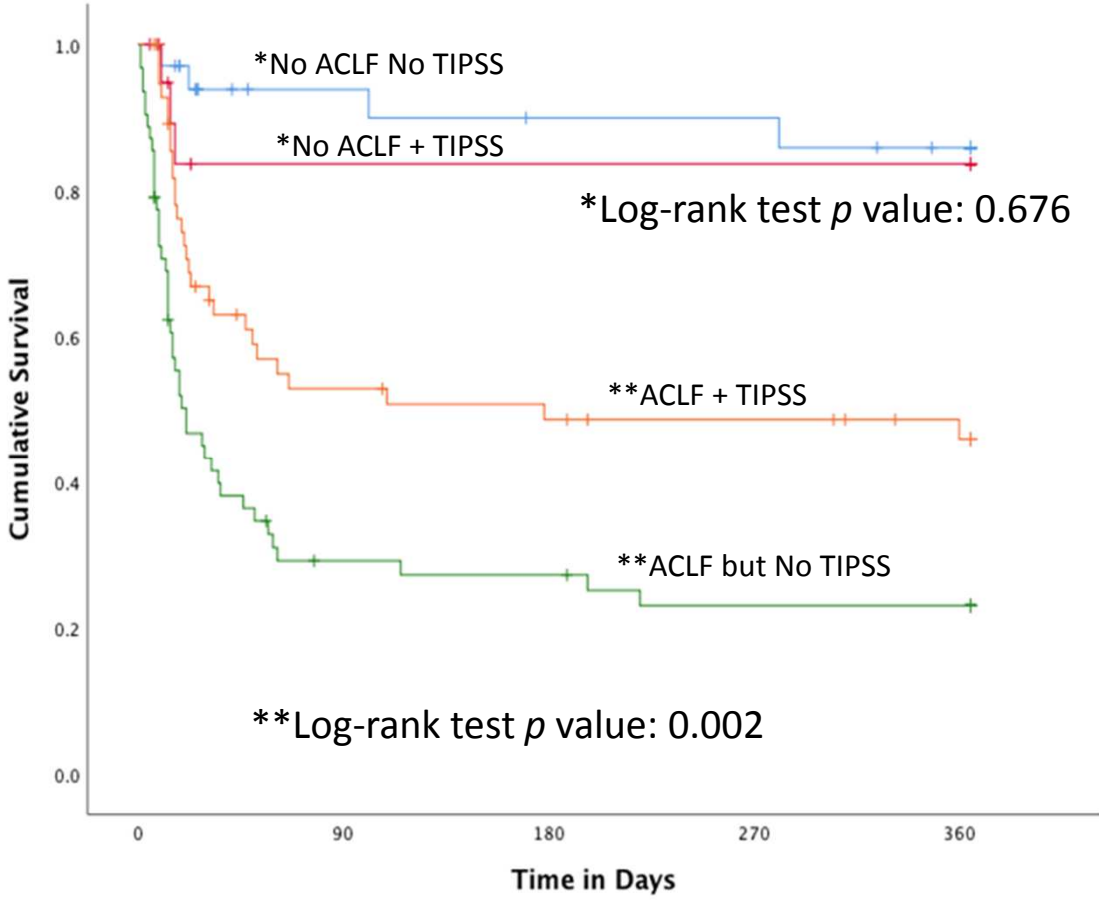
Accepted Date: 8 June 2020

Please cite this article as: Kumar R, Kerbert AJC, Sheikh MF, Roth N, Calvao JAF, Mesquita MD, Barreira AI, Gurm HS, Ramsahye K, Mookerjee RP, Yu D, Davies NH, Mehta G, Agarwal B, Patch D, Jalan R, Determinants of mortality in patients with cirrhosis and uncontrolled variceal bleeding, *Journal of Hepatology* (2020), doi: https://doi.org/10.1016/j.jhep.2020.06.010.

Mortality plateau's after 4 weeks in ACLF secondary to OGVB irrespective of grade of ACLF



Survival Of patients with ACLF secondary to OGVB is improved by TIPSS insertion



Determinants of mortality in patients with cirrhosis and uncontrolled variceal bleeding

Rahul Kumar[1,2,3], Annarein J.C. Kerbert[1], M. Faisal Sheikh[1], Noam Roth[4], Joana A.F. Calvao[1,7], Monica D. Mesquita[1,7], Ana I. Barreira[1,7], Haqeeqat S Gurm[1], Komal Ramsahye[1], Rajeshwar P. Mookerjee[1], Dominic Yu[5], Neil H. Davies[5], Gautam Mehta[1], Banwari Agarwal[1,4], David Patch[6] , Rajiv Jalan[1].

Authors' institutional affiliations:

1. Liver Failure Group, UCL Institute for Liver and Digestive Health, UCL Medical School, Royal Free Campus, London, UK

2. Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore

3. Duke- NUS Academic Medical Centre, CGH Campus, Singapore.

4. Intensive Care Unit, Royal Free Hospital London NHS Foundation Trust, London, UK

5. Department of Radiology, Royal Free Hospital London NHS Foundation Trust, London, UK

6. The Royal Free Sheila Sherlock Liver Centre, Royal Free London NHS Trust, London, UK

7. Centro Hospital de Tras-os-Montes e Alto Douro, EPE, Portugal

Corresponding author:

Rajiv Jalan MD, PhD

Liver Failure Group, UCL Institute for Liver and Digestive Health

Division of Medicine, UCL Medical School Royal Free Hospital,

Rowland Hill Street London, NW3 2PF, UK

E-mail: r.jalan@ucl.ac.uk

Phone: +442074332745

Keywords

Acute Oesophago-gastric variceal bleeding, Acute on chronic liver failure, Transjugular intrahepatic portosystemic shunt.

Running title: ACLF and TIPSS

Total number of words: 5153 (excluding references)

Number of tables:6

Number of figures: 2

(vi) **Conflict of interest statements:**

Rajiv Jalan has research collaborations with Yaqrit and Takeda. Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Ltd, a spin out company from University College London. He is also a Founder of Thoeris Ltd.

All the other authors do not have any potential conflict of interest to declare.

(vii) **Financial support statement:**

All the authors have no financial support statement to make.

(vi) **Authors' contributions:**

Concept: RJ, RK; Data Collection: RK, MFS, NR, JC, MM, AB, HSG, KR; Analysis: RK, AK; Interpretation: All; Manuscript Writing: RK, RJ; Critical Reviewing: All

Highlights:

1. Failure to control variceal bleeding in cirrhosis has high mortality, and also frequently causes ACLF.
2. Occurrence of ACLF is the most important determinant of 42-day (Hazard Ratio=4.5) and 1-year (Hazard Ratio=5.2) mortality in cirrhotic patients with failure to control variceal bleeding.
3. Insertion of transjugular intrahepatic stent-shunt improves 42-day and 1-year survival in patients with ACLF secondary to failure to control variceal bleeding.

Lay Summary:

Variceal bleeding that is not controlled by initial endoscopy is associated with high risk of death. The results of this study showed that in the occurrence of failure of the liver and other organs defines the risk of death. In these patients, insertion of a shunt inside the liver to drain the portal vein improves survival.

Abstract

Background and Aim: Failure to control oesophago-gastric variceal bleeding (OGVB) and acute-on-chronic liver failure (ACLF) are both important prognostic factors in liver cirrhosis. The aims of this study were to determine whether ACLF and its severity define the risk of death in OGVB and whether insertion of rescue transjugular intrahepatic stent-shunt (TIPSS) improves the survival of patients with failure to control OGVB and ACLF.

Methods: From a prospectively maintained ICU registry, data of 174 consecutive eligible patients with failure to control OGVB between 2005 and 2015, were included. Rescue TIPSS was defined as technically successful TIPSS within 72-hours of presentation with failure to control OGVB. Cox proportional hazards regression analyses were applied to explore the impact of ACLF and TIPSS on survival in failure-to-control OGVB.

Results: ACLF patients (n=119) were significantly older, had organ failures and higher white cell count compared with patients with acute decompensation (AD, n=55). Mortality at 42-days and 1-year was significantly higher in ACLF (47.9% and 61.3%) as compared to AD patients (9.1% and 12.7%, p<0.001), whereas there was no difference in the number of endoscopies and transfusion requirements between these groups. TIPSS was inserted in 78 patients [AD: 21 (38.2%); ACLF: 57 (47.8%), p=0.41]. In ACLF, rescue TIPSS insertion was an independent favorable prognostic factor for 42-day mortality. In contrast, rescue TIPSS did not impact on the outcome of AD patients.

Conclusions: This study shows for the first time that in patients with failure to control OGVB, the presence and severity of ACLF determines the risk of 42-day and

1-year mortality. Rescue TIPSS is associated with improved survival of ACLF patients.

Introduction

Variceal bleeding from oesophago-gastric varices (OGVB) is a common acute decompensating (AD) event in liver cirrhosis, which may result in acute-on-chronic liver failure (ACLF), a distinct clinical condition characterized by hepatic and extrahepatic organ failures and high-risk of short-term mortality [1], [2]. ACLF occurs in about 30% of patients with cirrhosis admitted with AD, and has a 28-day mortality of around 30-35%, compared with mortality rates of less than 15% in those without ACLF [1], [3]–[5]. Pathophysiologically, systemic inflammation is a dominant feature of ACLF [1], [6], [7].

Despite the recent advances in clinical management, upto 15% of patients with OGVB fail initial endoscopic hemostasis and over 20% rebleed within 6-weeks [8]–[11]. Mortality rates of 25-60% were observed in patients with failure of endoscopic therapy in various studies [12]–[14]. Patients who fail combined initial pharmacological and endoscopic management are bridged to a definitive therapy with help of either balloon or esophageal stent tamponade; these patients are termed “failure to control bleeders”. Failure to control bleeding is defined as failure to achieve hemostasis after either 2 endoscopic attempts or one endoscopy with use of bridging therapies like balloon or esophageal stent tamponade [9]–[11], [15], [16]. The treatment options in failure to control OGVB include repeat endoscopic treatment, TIPSS or surgery. TIPSS done in such scenario is termed as a “rescue of salvage TIPSS” which is different from an early pre-emptive TIPSS [9]–[11]. Data from several randomized controlled trials show that the insertion of pre-emptive TIPSS is associated with reduced risk of mortality. [12][17], [18] However, the benefit on mortality achieved by rescue TIPSS is less clear.

ACLF is characterized by markedly deranged systemic and hepatic hemodynamics, with severe portal hypertension and worsening systemic vasodilation [19]. This increase in portal pressure is largely a consequence of hepatic and systemic inflammation, reduced hepatic perfusion and increased intrahepatic resistance [20]. In patients with existing ACLF, higher levels of hepatic venous pressure gradient and lower hepatic blood flow has been demonstrated and therefore they are likely to be at significant risk of bleeding from OGVB [19]. TIPSS creates a vascular conduit between the systemic and portal circulation, leading to a rapid decline in portal pressure, which in turn results in rapid control of OGVB [21], [22]. Theoretically, insertion of a TIPSS in a patient with ACLF may worsen systemic hemodynamics and reduce hepatic perfusion even further [19], [23]. The usefulness of TIPSS in this population is currently unknown. Therefore, the aims of this study were to determine whether the presence of ACLF influences short and long-term mortality of cirrhotic patients with failure to control OGVB and whether early rescue TIPSS insertion in these patients with ACLF improves their survival.

Methods

Patient Selection and Management

The Royal Free Hospital (RFH) is a tertiary referral hospital in North-West London, which receives patients from neighboring hospitals and through its own emergency department. From a prospectively maintained registry of all patients with liver cirrhosis and acute decompensation admitted to the Intensive Care Unit (ICU) of the Royal Free Hospital (RFH), data of 174 consecutive “failure to control bleeders” between 2005 and 2015 were included. The definition used to identify “failure to control variceal bleeding” was adapted from the Baveno VI consensus: ‘in presence of full medical treatment (resuscitation, vasoactive drugs, antibiotics), either failure to control bleeding despite 2 attempts at endoscopic hemostasis or one attempt at endoscopic hemostasis with use of either rescue balloon tamponade of esophageal stent device within 5-days from the first episode’ [10], [11], [15], [16], [24]. Patient with a diagnosis of hepatocellular carcinoma or main portal vein thrombosis were excluded. (See Consort Diagram; Figure 1). Some of the patients in the database have been described in previous studies [25]–[27]. All patients were managed according to the standard of care for acute OGVB with a combination of volume resuscitation, vasoactive drugs, antibiotic prophylaxis, and endoscopic intervention. Full organ support was instituted as needed: vasopressors to maintain the mean arterial pressure (MAP) greater than 70 mmHg, renal replacement therapy (RRT) using continuous veno-venous hemofiltration was instituted in patients with renal failure who did not respond to terlipressin and albumin, and mechanical ventilation was provided for respiratory failure, airway protection, insertion of TIPSS and severe hepatic encephalopathy. After admission to ICU, patients were assessed for their suitability for further therapy. Decision for further rescue therapy including repeat

endoscopy and TIPSS was based on patient's overall condition, assessment of ongoing bleeding and contraindication to various therapies as assessed by the medical team. Any missing data from the registry was collected through archived clinical notes, charts and electronic repositories used for clinical care at our hospital.

Defining Variables

Clinical and biochemical parameters obtained after resuscitation on the day of admission to the ICU were used to diagnose organ failures and ACLF. Patients were diagnosed and classified as having AD (no ACLF) or ACLF based on the European Foundation for the Study of Chronic Liver Failure (CLIF) organ failure (CLIF-OF) scoring system, which is a modified version of sequential organ failure assessment (SOFA) score[1], [28]. Severity of hepatic encephalopathy (HE) was assessed using the West Haven criteria [29]. As all patients were being treated with prophylactic antibiotics, and chest x-ray often showed opacification due to aspiration, the diagnosis of infection was made on positive cultures of the blood, urine and sputum or a diagnosis of spontaneous bacterial peritonitis within first 48 hours of admission. Since ACLF itself can precipitate an episode of OGVB and patients who present with OGVB can develop ACLF, a differentiation was made. Patients with "ACLF prior to OGVB" refers to those patients who had been in hospital with diagnosed ACLF within the past 2 weeks and had an episode of OGVB after the diagnosis of ACLF. Rescue TIPSS was defined as insertion of TIPSS at the earliest opportunity (within 72 hours) after failed attempts at endoscopic hemostasis [9]–[11], [15], [16], [24] . The decision for insertion of TIPSS was physician-based, all patients included in the study were considered for rescue TIPSS at admission to ICU. After admission to ICU RFH, patients were offered full supportive care on an individualized basis. TIPSS

was performed using the Viatorr stents endoprosthesis, and was dilated to minimum of 8 mm with the aim to reduce the portal pressure gradient to less than 12mmHg or by 20% from baseline [14], [18]. In the period between failed endoscopy and TIPSS, patients were managed according to standard of care, which included but was not limited to use of balloon tamponade and/or esophageal stent as per, and prevailing practices and guidance [11]. Ongoing alcohol use was defined as significant consumption of alcohol within the last 3 months of admission. Non-selective beta-blocker (NSBB) use was defined as a valid prescription of NSBB (propranolol or carvedilol) prior to the admission. Re-bleeding was defined as any evidence of fresh bleeding (hemodynamic instability in presence of melena/hematemesis, hemoglobin drop of ≥ 3gm/dl) after 5 days of index bleeding in patients who did not receive TIPSS and any fresh bleeding after TIPSS insertion in patients who received TIPSS [10], [11], [24]. As the Baveno VI consensus recommends the use of 42-days survival to assess outcome [11] in patients with OGVB, this was the primary end point of choice in the current study. In addition, survival analysis for 28-days, 3 months and 1 year was performed. After discharge from the hospital, patients received their usual standard of care according to Baveno guidance [11], which was implemented by their respective physicians.

Statistical Analysis

The data were analyzed on an intention-to-treat basis. Normal distribution of the variables was first tested by quantile-quantile plot and histograms. Student's t-test was used for comparing normally distributed continuous variables, whereas variables showing skewed distributions with variance heterogeneity were evaluated using the Mann-Whitney U test. Pearson $\chi 2$ test was used to compare categorical variables. A

univariate Cox-proportional hazard regression analysis was performed to identify factors associated with 28-day, 42-day, 3-month and 1-year mortality. In order to identify the prognostic score with the best predictive ability for 42-day and 1-year mortality, a receiver operating characteristic (ROC) curve analysis was performed for the CTP, MELD-Na, UKELD and CLIF-C OF scores. The score with the highest area under the ROC (AUROC), was then entered in the multivariate analysis together with parameters with a $p<0.05$ in univariate analysis. Parameters included in the selected prognostic scores were excluded from multivariate analysis in order to avoid redundancy. Survival analysis at 42-days and 1-year stratified according to TIPSS placement and ACLF presence was performed using Kaplan-Meier and compared with the Log-rank test. Mortality was used as an endpoint and patients were censored at time of liver transplant or last patient contact. Because only 2 patients were transplanted in the whole cohort within the study period, liver transplant was not considered to be a competing risk. Normally distributed data are presented as mean ± standard deviation (SD), and nonparametric data are presented as median (interquartile range, IQR). A two-sided p value < 0.05 was considered statistically significant. The data was analysed using IBM SPSS version 26.

Results

Baseline patient characteristics and mortality

A total of 174 patients qualified for the study (Fig1: consort diagram). Of these, 55 patients had AD and 119 patients had ACLF following resuscitation on the day of ICU admission. Table 1 illustrates the baseline characteristics of all patients (n=174) including the AD [n=55, (31.6%)] and ACLF groups [n=119, (68.4%)].

Patients with ACLF were significantly different from AD, in being older (p=0.014), having more severe features of decompensation [p=0.002 for ascites and p<0.001 for hepatic encephalopathy (HE)] and, in correspondence to its definition, having higher incidence of organ failures (p<0.001). While hemoglobin, platelet count, serum sodium and albumin were not significantly different between the groups, white cell count (WCC) (p=0.025), international normalized ratio (INR) (p=0.001), serum bilirubin (p <0.001) and creatinine (p=0.001) levels were significantly raised in ACLF group. A total of 17 (9.8%) patients had positive microbiology, of which 15 (88.2%) were in the ACLF group and 2 (11.8%) in the AD group; this difference however was not statistically significant (p=0.064). Patients in both groups had a median of two endoscopies prior to inclusion, and the blood product requirements were similar in both groups. Higher Child-Turcotte-Pugh (CTP) class, MELD-Na, UKELD and CLIF-C OF scores were observed in ACLF group (p<0.001 for all). A total of 74 (42.5%) patients had presented with their first episode of OGVB of whom 59 (79.7%) presented with ACLF and 15 (20.3%) with AD (p=0.041). Similar proportion of patients in the AD and ACLF groups were on non-selective beta-blockers (NSBB) before the current OGVB. TIPSS was inserted in 78 patients; 21 (27%) had AD and 57 (73%) had ACLF (p=0.231).

Mortality in failure to control OGVB

A total of 59 (33.9%) patients at 28-days, 62 (35.6%) at 42-days, 72 (41.4%) at 3-months and 80 (45.9%) at 1 year died (Table 1). Mortality rates at 28-days, 42-days, 3-months and 1-year were significantly lower in AD as compared to ACLF (9.1%, 9.1%, 9.1%, 12.7% vs. 45.4%, 47.9%, 56.3%, 61.3%, all p<0.001). The risk of death at 28-days in both AD and ACLF group was similar to that at 42-days. Mortality increased with increasing ACLF grades (p<0.001).

Factors associated with 42-days mortality: All Patients

Table 2 illustrates the patient characteristics of the survivors and non-survivors at 42-days by which a total of 62 (35.6%) patients died. The survivors were younger (p=0.048), whereas HE grade (p=0.156) and severity of ascites (p=0.210) were similar. Respiratory rate (p=0.011), P/F ratio (p=0.032) and heart rate (p=0.004) were more severely deranged in the non-survivors. Higher levels of serum creatinine (p<0.001), total bilirubin (p<0.001), and WCC (<0.001) were observed in the non-survivors. Significantly more patients with microbial positivity died (p=0.003) within 42-days. Of the individual organ failures, liver (p=0.004), circulatory (p=0.014), coagulation (p=0.022), respiratory (p=0.027) and renal failures (p <0.001) but not cerebral failure (p=0.056) were significantly different between the survivors and non-survivors. Non-survivors required significantly more FFP (p=0.022) and platelet (p=0.013) transfusions while the requirement of packed red cells was similar (p=0.325).

Presence of ACLF (p<0.001) and its severity in terms of ACLF grade (p <0.001) were associated with 42-day mortality, and significantly more patients in the non-

survivor group had ACLF prior to variceal bleeding (p<0.001). Non-survivors had higher CTP class (p=0.004), MELD-Na (p <0.001), UKELD (p <0.001) and CLIF-OF scores (p<0.001). Significantly more patients presenting with index OGVB died within 42-days compared to patients who had bled previously (p=0.015). Of the 56 patients who were on NSBB prescription, 45 (80.4%) survived and 11 (19.6%) died (p=0.006). The proportion of patients presenting with ongoing alcohol abuse was similar between survivors and non-survivors. In the overall cohort, a total of 78 patients received TIPSS.

On univariate Cox regression analysis of variables (Table 2), significant differences were found between 42-day survivors and non-survivors, such that age, respiratory rate, P/F ratio, heart rate, WCC, total serum bilirubin, serum creatinine, microbial positivity, fresh frozen plasma and pooled platelet transfusion requirements, organ failures (liver, renal, coagulation, circulatory and respiratory), presence and grade of ACLF, CTP class, MELD-Na, UKELD and CLIF OF scores, index OGVB, no prior NSBB use (p=0.031) and ACLF prior to OGVB (p<0.001) were predictors of mortality. TIPSS insertion had no survival advantage in the overall cohort which included both AD and ACLF patients.

Of the CTP, MELD-Na, UKELD and CLIF-C OF scores for predicting 42-day mortality, CLIF-C OF score had the best AUROC of 0.789 (Supplementary Figure 1A). Therefore, multivariate models were created based CLIF-OF score and other variable which came out as significant in univariable analysis.

Three multivariate models were computed (table 3). The first model was created using the CLIF-C OF score, age, WCC, microbial positivity, transfusion requirements of fresh FFP and platelets and presence of ACLF prior to current episode of OGVB. In this multivariate analysis of all patients (N=174), age (HR:1.032; 95%CI:1.007-1.058, p=0.012), WCC (HR:1.047; 95%CI:1.005-1.090, p=0.027), microbial positivity (HR:2.512; 95%CI: 1.278-4.941, p=0.008), and CLIF-C OF score (HR:1.318; 95%CI:1.120-1.550, p=0.001) were independent predictors of 42-day mortality.

In a second multivariate model (Table 3) which was based on age, WCC, positive microbiology, transfusion requirement of FFP and platelets and a diagnosis of ACLF, age (HR:1.026; 95%CI:1.002-1.051, p=0.035), WCC (HR:1.056; 95%CI:1.017-1.097, p=0.006), positive microbiology (HR:2.906; 95%CI:1.518-5.561, p=0.014 and a diagnosis of ACLF (HR:4.580; 95%CI:1.800-11.635, p=0.001) were independent predictors of 42-day mortality. As information about microbial positivity and transfusion requirements are not available early in the course of a patient's with OGVB, a third model (Table 3) was created with factors available at the time of ICU admission. In this model including age, WCC, CLIF-OF score and ACLF prior to OGVB; age (HR:1.023; 95%CI:1.003-1.051, p=0.026), WCC (HR:1.046; 95%CI:1.004-1.090, p=0.033) and CLIF-C OF score (HR:1.289; 95%CI:1.102-1.508, p=0.001) were independent predictor of 42-days mortality.

Factors associated with 1-year mortality: All Patients

The factors associated with 1-year mortality in the entire patient cohort were similar to that predicting 42-day mortality (Supplementary Table 1). A total of 80 (46%) patients died at 1-year follow up.

Of CTP, MELD-Na, UKELD and CLIF-C OF scores for predicting 1-year mortality, CLIF-C OF score had the best AUC of 0.815 (Supplementary Figure 1B) and was thus selected for multivariate modelling with other factors that stood out in univariate analysis. Three multivariate models were computed (table 4), with and without the consideration of the presence and severity of ACLF. In the first multivariate model age (HR: 1.034; 95%CI 1.013 -1.056, p=0.001), ACLF prior to OGVB (HR: 2.306; 95%CI 1.226-4.338, p=0.010) and CLIF-C OF score (HR: 1.306; 95%CI 1.133-1.504, p<0.001) were independent predictors of 1-year mortality.

The second model using presence of ACLF as one of the factors with age, WCC, positive microbiology and transfusion requirements of FFP, age (HR: 1.030; 95%CI 1.009 -1.052, p=0.004), WCC (HR: 1.044; 95%CI 1.008-1.081, p=0.017), FFP transfusion (HR 1.053; 95%CI 1.006-1.103) and presence of ACLF (HR: 5.174; 95%CI 2.350-11.390, p<0.001) were independent predictors of 1-year mortality. In a third multivariate model of factors available at ICU admission which involved age, WCC, ACLF prior to OGVB and CLIF-OF score; age (HR: 1.034; 95%CI 1.013 - 1.056, p=0.002), ACLF prior to OGVB (HR: 2.462; 95%CI 1.326-4.571, p<0.004), and CLIF-C OF score (HR:1.304; 95%CI 1.139-1.492,p<0.001) were the independent predictors of 1-year mortality.

Factors associated with 42-day mortality in patients with ACLF

A total of 119 patients had ACLF at the time of inclusion in the study, of whom 57 (47.9%) died by 42-days (Supplementary Table 2). The survivors were younger (p=0.025). Presence or severity of HE (p=0.094) and ascites (p=0.863) were similar

between survivors and non-survivors. Respiratory rate was higher in non-survivors (p=0.024) but the P/F ratio was similar (p=0.846). Higher serum creatinine (p<0.001), total bilirubin (p=0.004) and WCC (p=0.003) was observed in non-survivors. Microbial positivity was more frequent in non-survivors (p=0.035). Of the individual organ failures, only renal failure (p <0.001) was significantly different between 42-day survivors and non-survivors. There was no difference in the transfusion requirements between the groups.

ACLF severity (p<0.001) was significantly associated with 42-day mortality (Figure 2A) and significantly more patients in the non-survivor group had “ACLF prior to OGVB” (p<0.001). CTP grade was not different between the survivors and non-survivors (p=0.160). Non-survivors had higher MELD-Na (p<0.001), UKELD (p=0.004), CLIF-OF (p<0.001) and CLIF-C ACLF (p<0.001) scores. Index OGVB (p=0.170) and ongoing alcohol abuse (p=0.119) were similar between 42-days survivors and non-survivors whereas use of NSBB prior to current episode of OGVB was higher in survivors (p=0.049). TIPSS procedure was performed in 57 (47.9%) patients of which 38 survived upto 42-days (p=0.012).

Univariate analysis of variables (Supplementary Table 2) significantly different between 42-days survivors and non-survivors in patients with ACLF revealed age, respiratory rate, WCC, total serum bilirubin, serum creatinine, renal failure, ACLF grade, ACLF prior to variceal bleeding, MELD-Na, UKELD, CLIF-C OF and CLIF-C ACLF score and TIPSS status (p=0.006) as being the predictors of 42-day mortality in patients with ACLF.

Fitting the commonly used prognostic scores i.e. MELD-Na, UKELD, and CLIF-OF score in the multivariate cox regression model and removing the potential confounders that were part of the predictive score calculations (MELD-Na, UKELD and CLIF-OF) (Table 5), for patients with ACLF (N=119); age (HR = 1.036; 95% CI 1.011 -1.062; p=0.005), CLIF-C OF score (HR = 1.226; 95% CI 1.010-1.488; p=0.039) and TIPSS status (HR = 0.540; 95% CI 0.309-0.943; p=0.030) were independent predictors of mortality (TIPPS insertion improved 42-days survival).

The ROC analysis of various scores in predicting 42-days mortality in ACLF patients showed CLIF-C ACLF score as the best predictor with AUROC of 0.774(95% CI: 0.692-0.862) (Supplementary figure 2A).

Factors associated with 1-year mortality in patients with ACLF

The factors associated with 1-year mortality in the patients with ACLF were similar to those predicting 42-day mortality (supplementary table 3). A total of 73 (61.3%) patients with ACLF died at 1-year follow up.

A multivariate model (Supplementary Table 4) was created using CLIF-OF score with age, ACLF prior to OGVB, and TIPSS status and showed that for patients with ACLF, age (HR = 1.042; 95% CI 1.019-1.065; p=0.001), CLIF OF score (HR = 1.234; 95% CI 1.045-1.458; p=0.013), ACLF prior to variceal bleeding (HR=2.525; 95% CI 1.350-4.724; p=0.004) and TIPSS insertion (HR = 0.519; 95% CI 0.320-0.841; p=0.008) were independent predictors of 1-year mortality.

ROC analysis of various scores in predicting 1-year mortality in ACLF patients showed CLIF-C ACLF score as the best predictor with AUROC of 0.793 (95%CI: 0.712-0.874) (Supplementary figure 2B).

Role of TIPSS in determining 42-day and 1-year survival

A total of 78 (44.8%) patients underwent TIPSS and 96 (55.2%) were managed without TIPSS insertion. The variables assessed between patients receiving TIPSS and those who did not, are illustrated in Table 6. There were no differences in age, gender, etiology of cirrhosis, clinical features (HE and ascites) or clinical parameters at presentation between the groups. Serum albumin (p=0.023) and serum creatinine (p=0.048) was marginally lower in patients receiving TIPSS. There was no difference in the microbial positivity, number of endoscopies prior to inclusion in the study, or in the bleeding episode being index OGVB. Transfusion of packed red cells (p=0.001) and fresh frozen plasma (p=0.029) in patients receiving TIPSS was higher. Presence of ACLF or its grade, CTP class, MELD-Na, UKELD and CLIF-C OF scores were also similar between the groups.

Of the 119 ACLF patients, 56 (47.1%) received TIPSS. A comparison of variables between the ACLF patients receiving TIPSS and those who did not is illustrated in supplementary table 5. Statistically significant differences were seen in serum creatinine levels, which was lower in patients receiving TIPSS (p=0.006). However, there was no difference in the organ failures including liver and renal between patients receiving or not receiving TIPSS. ACLF grade was also similar between the groups. MELD-Na (p=0.013) and CLIF -C ACLF (p=0.025) score were lower in the

subgroup of patients receiving TIPSS whereas CTP, UKELD and CLIF-OF scores were similar.

Supplementary table 6 illustrates the failure to control bleeding and the inpatient re-bleeding rates. In a total of 5 (2.8%) patients, satisfactory control of bleeding was not achieved in the first 5 days after their presentation with OGVB. All of them were in the non-TIPSS group. Another 28 (16.1%) patients experienced re-bleeding episodes during the inpatient stay, 7 (8.9%) in the TIPSS group and 21 (21.8%) in the non-TIPSS group, this difference was statistically significantly (p=0.021).

The survival function combining ACLF and TIPSS status and the survival times are illustrated in Supplementary Table 7 (42-days) and Supplementary Table 8 (1-year) respectively. Figure 2A and 2B represent the Kaplan Meier (KM) curve for 42-day and 1-year survival, stratified by ACLF grades, respectively. Figure 2C and 2D represent the KM curve for 42-day and 1-year survival, stratified according to ACLF and TIPSS status. Figure 2E and 2F represent the KM curve for 42-day survival of patients stratified accordingly to their TIPSS status and presence of ACLF. Of the 55 patients who had AD, 21 (38.2%) underwent TIPSS; 3 (14.3%) died within 42-days, and of the 34 (61.8%) AD patients who did not undergo TIPSS, 2 (5.9%) died (p=0.225). Of the 119 patients with ACLF, 57 (47.9%) underwent TIPSS; 20 (35.1%) of whom died within 42-days. Of the remaining 62 (52.1%) who did not receive TIPSS, 37 (59.7%) patients died (p=0.002). At 1-year of follow-up, of the AD patients, 3 (14.3%) with TIPSS and 4 (11.8%) without TIPSS died (p=0.676). Amongst the patients with ACLF, 26 (45.6%) patients with TIPSS and 47 (75.8%) patients without TIPSS had died (p=0.002) at 1-year. The cause of death of patients

who died in-hospital was available for 53 of 60 patients and is shown in supplementary table 9.

Discussion

The results of our study show for the first time that in patients with failure to control OGVB, the presence of ACLF and its severity are the key independent predictors of 42-day mortality with a hazard ratio of 4.5 (95% CI: 1.8-11.6) in multivariate modelling. Although rescue TIPSS insertion was not independently associated with lower 42-day and 1-year mortality in the whole cohort, mortality rates were significantly lower in ACLF patients who received rescue TIPSS as compared to those who did not. Moreover, rescue TIPSS was found to be an independent favorable prognostic factor in ACLF. These data are likely to have important clinical implications for the management of patients with failure to control OGVB.

In this study, which was specifically designed to address the risk of death in patients with failure to control OGVB admitted to the intensive care unit, the ACLF population is expectedly over-represented. The observed short-term mortality of patients included in this study is in keeping with the previously published data for patients with AD and ACLF, the former having a risk of death of less than 15% at 28-days [1]. However, OGVB as a precipitating event for the development of ACLF appears to have a different long-term outcome as mortality rate at 3-months was only about 10% higher than at 28-days. In contrast, in the CANONIC study, in which OGVB as a precipitating event is under-represented, mortality of ACLF patients at 3-months was markedly higher than at 28-days. The results of long-term survival data were similar to that in the present study in Hepatitis B-related ACLF, emphasizing the importance of the precipitating event in ACLF [5]. The most important observation in this paper was that the presence of ACLF was the strongest determinant of 28-day, 42-day, 3-month and 1-year mortality despite similarities in the number of endoscopies,

requirement of blood products, previous episodes of variceal bleeding, use of prophylactic NSBBs and treatment with TIPSS between the survivors and non-survivors.

Not surprisingly, greater proportion of ACLF patients had more marked organ dysfunction and failures, ascites, encephalopathy and higher CTP and MELD-Na scores. Age and WCC were higher in the ACLF patients, which were also independent predictors of mortality. Our observation is in keeping with the results of the CANONIC study, which was performed in acutely decompensated cirrhotic patients and also identified both age and WCC as independent predictors of mortality [28]. CLIF-OF score, age and WCC are components of the CLIF-C ACLF score, which has been shown to define the risk of death of patients with ACLF. Not surprisingly, this score performed the best in defining the risk of death of patients with OGVB and ACLF with an AUROC of 0.774 for 42-days and AUROC of 0.793 for 1-year.

Infection is known to be associated with poor outcome in patients with OGVB and administration of antibiotics prophylactically reduces mortality [16], [30], [31]. It was therefore not surprising to note that the presence of infection diagnosed by the presence of microbial positivity or spontaneous bacterial peritonitis within 48 hours to ICU was independently associated with risk of death. Because of the stringent criteria we used in this study to diagnose infection and the concomitant administration of antibiotics, it is likely that we have underestimated the prevalence of infection of these patients. These data are in keeping with previous studies, which

also show the important prognostic role of infection even in non-OGVB cirrhotic patients with AD and ACLF [2,4].

This study also provides new insights into the types of organ failures and their relevance in patients with high-risk OGVB. Although mortality was significantly greater in patients with any organ failure, the occurrence of renal failure was associated with the highest risk of death with a HR of 5.04 (95%CI: 2.97-8.52) at 42-days. In contrast, patients with AD had circulatory or respiratory failure in about 29% patients and yet their mortality rate was comparatively low supporting the notion that the failure of these organs in patients with OGVB are more likely to be recoverable. The high rate of circulatory failure in AD patients may represent hemodynamic compromise resulting from blood loss that is readily correctable. The relatively good outcome of respiratory failure may be because OGVB often results in aspiration and transfusion associated acute lung injury, which seem to have better prognosis than adult respiratory distress syndrome or severe pneumonia. It is important to note that the diagnosis of respiratory failure in this study was made using P/F ratios rather than need for mechanical ventilation as used by the NACSELD group, which, as we observe in this study overestimates the presence of respiratory failure [3]. We show that in this population, 90.8% were mechanically ventilated whereas only 43.6% had evidence of respiratory failure.

The observation that TIPSS insertion was independently associated with survival benefit in the patients with ACLF adds to the previously published papers, which have shown benefit of early pre-emptive TIPSS in patients with Child Class B and C patients and those with evidence of bleeding at endoscopy[14], [18], [32]. A recently

published multicenter retrospective study looked at the interaction of pre-emptive TIPSS and ACLF and found that rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPSS [33]. It is important to distinguish that the patients in our study are different to those described previously as our patients had failed endoscopic therapy and comprise a group that needed intensive care support. Our study shows that rescue TIPSS not only effectively controls bleeding in these patients with ACLF but also significantly increase their long-term survival. The selection of patients for TIPSS was left to the judgement of the physician in charge and no specific selection criteria were used. Patients undergoing TIPSS required more blood products compared with those that were not, making selection bias unlikely.

The other important findings of our study based on the univariate analysis was that the index variceal bleeders who developed ACLF, died more often than patients who had a previous variceal bleed, an observation that is similar to that in the CANONIC study, where patients with previous decompensation had a lower risk of death at 28-days [1]. Alternatively, this observation of lower mortality may be due to ongoing use of NSBB, which has been shown to have a protective effect on 42-day and 1-year mortality [34]. The presence of ACLF up to 2-weeks prior to OGVB worsened 42-day (HR: 4.4; 95%CI 2.6-7.4; $p<0.001$) and 1-year (HR: 5.3; 95%CI 3.3-8.6; $p<0.001$) mortality and was often the terminal event. Indeed, none of the patients who had failure to control OGVB on the background of existing ACLF grade 2 or 3 survived irrespective of their TIPSS status.

The results of this study have important clinical implications for patients with failure to control OGVB. First, the presence of ACLF and its severity measured by CLIF-C ACLF score allows risk stratification of these patients and this score has been validated for sequential use [28]. In those that do not improve after 5-7 days, early liver transplantation may be desirable. In those that recover, good long-term survival can be expected arguing strongly for providing these patients with intensive care support. Second, the survival benefit of TIPSS in patients with ACLF makes a strong case for rapid and safe transfer of such patients to the referral centers. In contrast, the occurrence of failure to control OGVB on the background of advanced grades of ACLF is likely to represent a terminal event and consideration should be given to palliative care for such patients. Finally, the occurrence of respiratory or circulatory failure in patients with ACLF due to precipitants other than OGVB is considered a poor prognostic sign [35], however, the failure of these organs is common in patients with OGVB and should not detract from aggressive management.

The data described in this paper must be interpreted in light of some of the limitations of this study. First, the weakness introduced by the retrospective nature of the study is partially overcome by the fact that the data is maintained in a carefully controlled registry in our intensive care unit. Second, although the study comes from a single center over a 10-year period, it provides real-world data of patients transferred from a large referral base around London. Third, although the fact that the decision to perform TIPSS was physician based rather than protocolized is a potential limitation, it provided two cohorts, one with and the other without TIPSS allowing assessment of its potential role in this unique patient population. Finally, our

study includes only the failure to control OGVB patients who required intensive care, and therefore, the result cannot be applied to all patients with OGVB.

In conclusion, this study shows for the first time that, in patients with failure to control OGVB, the presence and severity of ACLF, age and systemic inflammation reflected by WCC, determines the risk of 28-day, 42-day and 1-year mortality. In patients with ACLF, rescue TIPSS improves survival significantly and should be offered to these patients.

References

[1] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis. Gastroenterology 2013; 144 (7): 1426-1437.

[2] García-Pagán J, Reverter E, Abraldes J and Bosch J. Acute variceal bleeding. Seminars in Respiratory and Critical Care Medicine 2012; 33: 46-54.

[3] Bajaj J, O'Leary J, Reddy K, Wong F, Biggins S, Patton H, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014; 60(1): 250-256.

[4] Sargenti K, Prytz H, Nilsson E, and Kalaitzakis E. Predictors of mortality among patients with compensated and decompensated liver cirrhosis: The role of bacterial infections and infection-related acute-on-chronic liver failure. Scandinavian Journal of Gastroenterology 2015; 50(7): 875-883.

[5] Li H, Chen LY, Zhang N, Shu TL, Zeng B, Pavesi M, et al. Characteristics, Diagnosis and Prognosis of Acute-on-Chronic Liver Failure in Cirrhosis Associated to Hepatitis B. Scientific Reports 2016; 6: 25487.

[6] Cl J, Stauber R, Coenraad M, Moreau R, Jalan R, Pavesi M, et al. Systemic Inflammation in Decompensated Cirrhosis: Characterization and Role in Acute-on-Chronic Liver Failure. Hepatology 2016; 64(4): 1249-64.

[7] Bernsmeier C, Pop O, Singanayagam A, Triantafyllou E, Patel V, Weston C, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. Gastroenterology 2015; 148(3): 603-615.

[8] Augustin S, Muntaner L, Altamirano JT, Gonzalez A, Saperas E, Dot J, et al. "Predicting Early Mortality After Acute Variceal Hemorrhage Based on Classification and Regression Tree Analysis. Clinical Gastroenterology and Hepatology 2009; 7(12):1347-1354.

[9] Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee R, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. Journal of Hepatology, 2018; 69(2): 406-460.

[10] de Franchis R, On behalf of the Baveno V Faculty. Revising consensus in portal hypertension: Report of the Baveno v consensus workshop on methodology of diagnosis and therapy in portal hypertension. Journal of Hepatology, 2010: 53(4): 762-768.

[11] de Franchis R, Abraldes J, Bajaj J, Berzigotti A, Bosch J, Burroughs A, et al. Expanding consensus in portal hypertension Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. Journal of Hepatology 2015;63: 743–752.

[12] D'Amico G, de Franchis R, and a Cooperative Study Group. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology 2003; 38 (3): 599-612.

[13] Bosch J, Thabut D, Bendtsen F, D'amico G, Albillos A, Abraldes JG, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: A randomized, double-blind trial. Gastroenterology 2004; 127(4): 1123–1130, 2004.

[14] García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al. Early Use of TIPS in Patients with Cirrhosis and Variceal Bleeding. N Engl J Med. 2010; 362: 2370-2379

[15] Njei B, McCarty T and Laine L. Early transjugular intrahepatic portosystemic shunt in US patients hospitalized with acute esophageal variceal bleeding. Journal of Gastroenterology and Hepatology 2017; 32(4): 852–858.

[16] Garcia-Tsao G, Abraldes J, Berzigotti A, and Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017; 65 (1): 310-335.

[17] Garcia-Pagán JC, Pascoli M, Caca K, Laleman W, Bureau C, Appenrodt B, et al. Use of early-TIPS for high-risk variceal bleeding: Results of a post-RCT surveillance study. Journal of Hepatology 2013; 58(1): 45-50.

[18] Orloff M, Vaida F, Haynes K, Hye R, Isenberg J, and Jinich-Brook H. Randomized Controlled Trial of Emergency Transjugular Intrahepatic Portosystemic Shunt Versus Emergency Portacaval Shunt Treatment of Acute Bleeding Esophageal Varices in Cirrhosis. Journal of Gastrointestinal Surgery 2012; 16(11): 2094-2111.

[19] Mehta G, Mookerjee RP, Sharma V and Jalan R. Systemic inflammation is associated with increased intrahepatic resistance and mortality in alcohol-related acute-on-chronic liver failure. Liver International 2015; 35(3): 724-734.

[20] Mehta G, Gustot T, Mookerjee RP, Garcia-Pagan JC, Fallon M, Shah V, et al. Inflammation and portal hypertension-The undiscovered country. Journal of Hepatology 2014; 61: 155-163.

[21] Rössle M. TIPS: 25 years later. *Journal of Hepatology* 2013; 59(5):1081-1093.

[22] Silva-Junior G, Turon F, Baigas A, Cerda E, Garcia-Caiado A, Blasi A, *et al.* Timing Affects Measurement of Portal Pressure Gradient After Placement of Transjugular Intrahepatic Portosystemic Shunts in Patients With Portal Hypertension. *Gastroenterology 2017*; 152(6): 1358-1365.

[23] Lotterer E, Wengert A, and Fleig W. Transjugular Intrahepatic Portosystemic Shunt: Short-Term and Long-Term Effects on Hepatic and Systemic Hemodynamics in Patients With Cirrhosis. Hepatology 1999; 29 (3): 632-639.

[24] de Franchis R on behalf of the Baveno IV. Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of Hepatology* 2005; 43(1) 167-176.

[25] Engelmann C, Thomsen K, Zakeri N, Sheikh M, Agarwal B, Jalan R, *et al.* Validation of CLIF-C ACLF score to define a threshold for futility of intensive care support for patients with acute-on-chronic liver failure. *Critical Care 2018*; 22: 254

[26] Figorilli F, Putignano A, Roux O, Houssel-Derby P, Francoz C, Paugam-Burtz C, *et al.* Development of an organ failure score in acute liver failure for transplant selection and identification of patients at high risk of futility. *PLoS ONE 2017;* 12(12): e0188151.

[27] Shalimar, Sheikh MF, Mookerjee RP, Agarwal B, Acharya SK and Jalan R. Prognostic Role of Ammonia in Patients With Cirrhosis. *Hepatology 2019;* 70(3): 982-994.

[28] Jalan R, Saliba F, Pavesi M, Amoros A, Mareau R, Gines P, *et al.* Development and validation of a prognostic score to predict mortality in

patients with acute-on-chronic liver failure. *Journal of Hepatology* 2014; 61(5), 1038-1047.

[29] Conn H, Leevey C, Vlahcevic Z, Vlahcevic ZR, Rodgers JB, Maddrey WC, *et al.* Comparison of Lactulose and Neomycin in the Treatment of Chronic Portal-Systemic Encephalopathy: A double blind controlled trial. *Gastroenterology 1977;* 72(4); 573-583.

[30] Goulis J, Patch D and Andrew K Burroughs. Bacterial infection in the pathogenesis of variceal bleeding, Lancet 1999; 353:139-42.

[31] Jalan R, Fernandez J, Weist R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013. Journal of Hepatology 2014; 60(6):1310-1324.

[32] Azoulay D, Castaing D, Majno P, Saliba F, Ichai P, Smail A, et al. Salvage transjugular intrahepatic portosystemic shunt for uncontrolled variceal bleeding in patients with decompensated cirrhosis. Journal of Hepatology 2001; 35: 590-597.

[33] Trebika J, Gu W, Ibanez-Samaniego L, V.Hernandez-Gea, C. Pitarch, E. Garcia, et al. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. Journal of Hepatology 2020; doi: 10.1016/j.hep.2020.02.024.

[34] Mookerjee RP, Marco P, Thomsen KL, Mehta G, Macnaughtan J, Bendtsten F, et al. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. Journal of Hepatology 2015; 64(3); 574- 582.

[35] Sundaram V, Jalan R, Wu T, Volk M, Asrani S, Klein A, et al. Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver

Failure Before and After Liver Transplantation. Gastroenterology 2019; 156(5): 1381-1391.

Legends to Figures

Figure 1: Patient Selection Consort Diagram

Abbreviations: GI: Gastro-intestinal; TIPSS: Transjugular Intrahepatic Portosystemic Shunt

Figure 2 (A-F) Kaplan-Meier 42-days and 1-year survival curves by ACLF grade and combined ACLF and TIPSS status and the influence of TIPSS and ACLF on 42-days mortality.

Panel 2A: Kaplan-Meier 42-days survival function by ACLF grade

Panel 2B: Kaplan-Meier 1-year survival function by ACLF grade

Panel 2C: Kaplan-Meier 42-days survival function by combined ACLF and TIPSS status

Panel 2D: Kaplan-Meier 1-year survival function by combined ACLF and TIPSS status

Panel 2E: Kaplan Meier 42-days survival function by presence of ACLF.

Panel 2F: Kaplan Meier 42-days survival function by TIPSS insertion

Abbreviations: ACLF: Acute on Chronic Liver Failure; TIPSS: Transjugular Intrahepatic Portosystemic Shunt

Study Highlights:

1. Failure to control variceal bleeding in cirrhosis has high mortality, and also frequently causes ACLF.
2. Occurrence of ACLF is the most important determinant of 42-day (Hazard Ratio=4.5) and 1-year (Hazard Ratio=5.2) mortality in cirrhotic patients with failure to control variceal bleeding.
3. Insertion of transjugular intrahepatic stent-shunt improves 42-day and 1-year survival in patients with ACLF secondary to failure to control variceal bleeding.

Figure 1: Consort Diagram

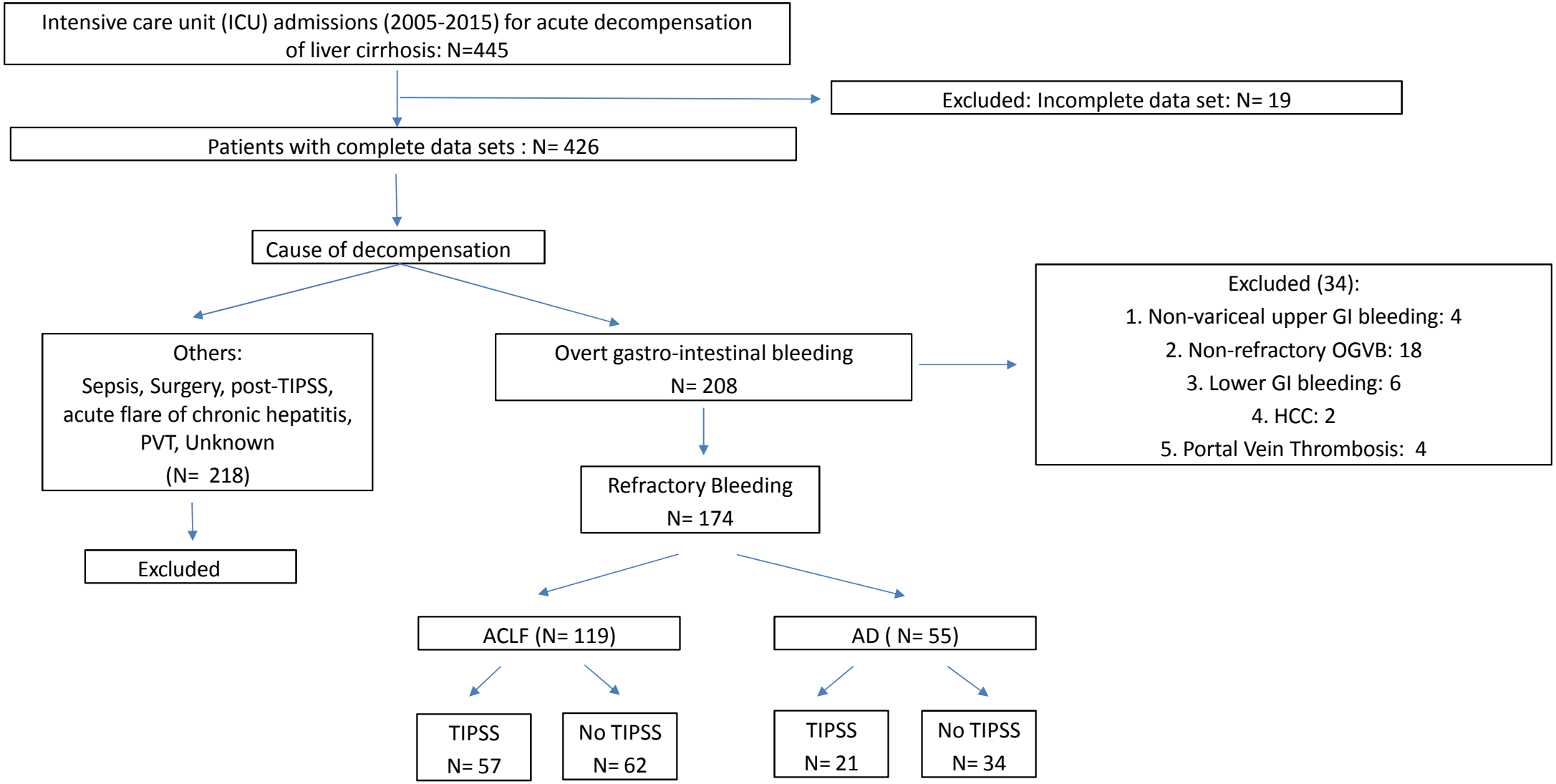


Table 1. *Patient characteristics

Variable	All patients (N= 174)	AD (n= 55 (31.6%))	ACLF (n= 119 (68.4%))	P-value
Age (years)	51.5 ± 11.7	48.3 ± 12.2	52.9 ± 11.3	0.014
Male gender, n (%)	134 (77)	44 (80)	90 (75.6)	0.524
Etiology of cirrhosis, n (%)				0.574
Alcohol	106 (60.9)	33 (63.6)	71 (59.7)	
HBV	3 (1.7)	2(3.7)	1(0.8)	
HCV	10 (5.7)	4(7.4)	6(5)	
NAFLD	7 (4)	2(3.7)	5(4.2)	
PBC/PSC/AIH	13 (6.9)	3(5.6)	9(7.5)	
Cryptogenic	7 (4)	2(3.7)	5(4.2)	
Viral + ALD	19 (10.9)	3(5.6)	16 (13.3)	
Other	9 (5.2)	3(5.6)	6(5)	
Clinical features at presentation, n (%)				
Ascites				0.002
None	59 (33.9)	29 (52.7)	30 (25.2)	
Mild-Moderate	54 (31)	11(20.0)	43 (36.1)	
Severe	61 (35.1)	15 (27.3)	46 (38.7)	
Hepatic encephalopathy, n (%)				<0.001
None	51 (29.3)	33 (60.0)	18 (15.1)	
Grade 1 and 2	96 (55.2)	20 (36.4)	76 (63.9)	
Grade 3 and 4	27 (15.5)	2(3.6)	25 (21.0)	
Clinical parameters at presentation				
Temperature (^{o}C)	36.5 (36 - 37.1)	36.7 (36.3-37.2)	36.5(35.8-37.0)	0.075
Mean Arterial Pressure (mmHg)	77 (70 - 87)	80 (70-87)	77 (70-87)	0.618
Respiratory Rate (/min)	14 (12-16)	14 (12-15)	15 (12-16)	0.026
P/F Ratio (PaO2/Fi02 ratio)	222 (141-308)	274 (237 - 349)	169 (120-261)	<0.001
Heart Rate (HR) (/min)	91 ± 18	86 ± 15	93 ± 18	0.026
Laboratory values				
Haemoglobin (g/dl)	8.9 ±1.7	8.8 ± 1.5	9.01 ± 1.8	0.508
Platelet Count (x10^{9}/L)	68 (47-93)	61(44 -81)	69 (48 - 98)	0.109
White cell count (WCC) (x10^{6}/L)	9.0 (6.3-12.4)	8.1 (5.1-11.6)	9.4 (6.6 -13.6)	0.025
International Normalised Ratio (INR)	1.6(1.4-2.0)	1.5(1.4-1.8)	1.7 (1.5-2.2)	0.001
Total Bilirubin (mg/dl)	3.6 (1.7-6.7)	2.2 (1.2- 4.1)	4.5 (1.9 - 8.6)	<0.001
Albumin (g/dL)	24 ± 6	25 ± 6	24 ± 6	0.755
Creatinine (mg/dL)	0.9 (0.6-1.3)	0.7 (0.6 - 1.0)	1.0 (0.7-1.5)	<0.001
Sodium (mmol/L)	141 ± 6	142 ± 5	141 ± 7	0.288
< **Microbial positivity, n (%)**	17 (9.8)	2 (3.6)	15 (12.6)	0.064
& **Blood product requirement**				
Packed Red Cells (units)	8 (4-12)	8 (3-11)	8 (5-12)	0.220
Fresh Frozen Plasma (units)	5(2.75-8)	4(2-8)	5(3-8)	0.106
Platelets (units)	2 (1-4)	2(1-3)	2(1-4)	0.708
@ **Organ failures, n (%)**				
Liver	18 (10.3)	0	18 (15.1)	0.002
Renal	26(14.9)	0	26 (21.8)	<0.001
Cerebral	27 (15.5)	2 (3.6)	25 (21.0)	0.003
Coagulation	25(14.4)	0	25 (21.0)	<0.001

Circulatory	82(47.2)	12 (21.8)	70 (58.8)	<0.001
Respiratory	76(43.6)	4 (7.3)	72 (60.5)	<0.001
# Mechanical ventilation, n (%)	158 (90.8)	45 (81.8)	113 (95.0)	0.005
ACLF grades				
No ACLF	55 (31.6)	55 (100)	-	-
ACLF 1	30 (17.2)	-	30 (25.2)	-
ACLF 2	59 (33.9)	-	59 (49.6)	-
ACLF 3	30 (17.2)	-	30 (25.2)	-
Scores				
Child-Turcotte- Pugh Class				<0.001
A (5-6)	3 (1.7)	1 (1.8)	2 (1.8)	
B (7-9)	64 (36.8)	35 (63.6)	29 (24.3)	
C (10-15)	107 (61.5)	19 (34.5)	88 (73.9)	
MELD-Na	19(15-25)	17(13-18)	21(16-27)	<0.001
UKELD	53(49-58)	51(47-54)	55 (50 - 60)	<0.001
CLIF-C OF	10(9-12)	8 (7-9)	11 (10-12)	<0.001
CLIF-C AD	-	48 (42 - 53)	-	-
CLIF-C ACLF	-	-	52 (46 -58)	-
TIPSS insertion, n (%)	78 (44.8)	21 (38.2)	57 (47.8)	0.231
^ No. of endoscopies prior to inclusion	2 (2-3)	2(2-3)	2 (2-3)	0.798
Index OGVB, n (%)	74 (42.5)	15 (27.3)	59 (49.6)	0.041
NSBB use prior to current episode of OGVB, n (%)	56 (32.2)	23 (41.8)	33 (27.7)	0.064
@@ **Ongoing alcohol use (%)**	99 (56.9)	26 (47.3)	73 (61.3)	0.081
$$ **ACLF prior to current episode of OGVB (%)**	28 (16.1)	0	28 (23.5)	<0.001
Length of Stay				
Length of Stay in ICU (days)	6 (2-11)	3 (2-8)	7 (3-12)	0.009
Length of Stay in hospital (days)	14 (8-22)	11 (7-22)	15 (9-23)	0.079
Survival data				
28- days Mortality, n (%)	59 (33.9)	5 (9.1)	54 (45.4)	<0.001
42-days Mortality, n (%)	62 (35.6)	5 (9.1)	57 (47.9)	<0.001
3-months mortality, n (%)	72 (41.4)	5 (9.1)	67 (56.3)	<0.001
1-year mortality, n (%)	80 (45.9)	7 (12.7)	73 (61.3)	<0.001
ICU Survival, (alive, n, %)	131 (75.3)	52 (94.5)	79 (60.3)	<0.001
Hospital Survival (alive, n, %)	114 (65.5)	51 (92.7)	63 (55.3)	<0.001

*Following resuscitation on day of ICU admission

< Microbial positivity of samples collected within first 48 hours of admission including positive cultures of the blood, urine and sputum or a diagnosis of spontaneous bacterial peritonitis.

& From the time of presentation with OGVB till discharge from ICU or death which-ever is earlier.

@ Organ failures were defined based on method described by Moreau et al. (1)

Mechanical ventilation done within 24 hours of OGVB for either for respiratory failure, high grade hepatic encephalopathy, air-way protection or a combination of these factors.

^ This represents the total number endoscopies the patient has had before admission to RFH ICU

@@ ongoing alcohol abuse is defined by alcohol abuse in 3 months preceding OGVB

$$ Presence of ACLF In preceding 2 weeks.

West-Haven criteria was used to categorise hepatic encephalopathy. (2)

Abbreviations: ACLF: Acute on chronic liver failure; AD: Acute decompensation of liver cirrhosis; AIH: Auto-immune hepatitis; ALD: Alcoholic liver disease; CLIF: European Foundation for the study of chronic liver failure; HBV: Hepatitis-B virus; HCV: Hepatitis-C virus; ICU: Intensive care unit; MELD-Na: Model for End-Stage Liver Disease-sodium; NAFLD: Non-alcoholic liver disease; OF: Organ failure; OGVB: Oesophago-gastric variceal bleeding; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; NSBB: Non-selective beta blockers; TIPSS: Transjugular intrahepatic portosystemic shunt; VBL: Variceal band ligation.

Categorical variables are displayed in percent and continuous variables as mean ± SD (for Normally distributed data) or median (IQR) (Nonparametric testing for skewed data). Chi-square test was used for categorical variables, paired t-test for normally distributed continuous variable and Mann-Whitney U test was used for Non-parametric testing.

Table 2. * Factors associated with 42-day mortality in the whole patient cohort

Variable	All patients (N= 174)	Survivors N=112 (64.4%)	Non-Survivors N=62 (35.6%)	P value	Univariate Cox-regression	
					HR (95% CI)	P value
Age (years)	51.5 ± 11.7	50.1± 11.4	53.7 ±12.3	0.048	1.023 (1.002-1.045)	0.033
Male gender, n (%)	134 (77)	89 (79.5)	45 (72.6)	0.301		
Etiology of cirrhosis, n (%)				0.041	1.044(0.955-1.142)	0.342
Alcohol	106 (60.9)	76 (67.9)	30 (48.4)			
HBV	3 (1.7)	2 (1.8)	1 (1.6)			
HCV	10 (5.7)	5 (4.5)	5 (8.1)			
NAFLD	7 (4)	2 (1.8)	5 (8.1)			
PBC/PSC/AIH	13 (7.4)	4 (3.6)	9 (14.5)			
Cryptogenic	7 (4)	5 (4.5)	2 (3.2)			
Viral + ALD	19 (10.9)	12 (10.7)	7 (11.3)			
Other	9 (5.2)	6 (5.4)	3 (4.8)			
Clinical features at presentation, n (%)						
Ascites				0.210		
None	59 (33.9)	43(38.4)	16 (25.8)			
Mild-Moderate	54 (31)	31 (27.7)	23 (37.1)			
Severe	61 (35.1)	38 (33.9)	23 (37.1)			
Hepatic encephalopathy, n (%)				0.156		
None	51 (29.3)	35 (31.3)	16 (25.8)			
Grade 1 and 2	96 (55.2)	64 (57.1)	32 (51.6)			
Grade 3 and 4	27 (15.5)	13 (11.6)	14 (22.6)			
Clinical parameters at presentation						
Temperature (^{o}C)	36.5 (36 - 37.1)	36.6 (36 - 37.2)	36.5 (35.7-37.0)	0.251		
Mean Arterial Pressure (mmHg)	77 (70 - 87)	80 (70 -87)	75 (70-83)	0.089		
Respiratory Rate (/min)	14 (12-16)	14 (12-15)	15 (13-18)	0.011	1.130(1.070-1.194)	<0.001
P/F Ratio (PaO2/Fi02 ratio)	222 (142-308)	235 (156-322)	181 (122-289)	0.032	0.997 (0.994-1.000)	0.021
Heart Rate (HR) (/min)	91 ± 18	88 ±16	96 ±19	0.004	1.020 (1.006-1.034)	0.006
Laboratory values						
Haemoglobin (g/dl)	8.9 ±1.7	9.0 ± 1.6	8.9 ± 1.8	0.775		
Platelet Count (x10^{9}/L)	68 (47-93)	69 (47-89)	67 (47-108)	0.255		
White cell count (WCC) (x10^{6}/L)	9.0 (6.3-12.4)	8.1 (5.8 - 11.0)	11.8 (8.0 - 17.5)	<0.001	1.086 (1.046-1.128)	<0.001
International Normalised Ratio (INR)	1.6 (1.4-2.0)	1.6 (1.4-1.9)	1.8 (1.4-2.2)	0.061		

Total Bilirubin (mg/dl)	3.6 (1.7-6.8)	2.6 (1.4 - 5.4)	5.8 (3.1-9.2)	<0.001	1.057(1.030-1.086)	<0.001
Albumin (g/dL)	24 ± 6	25 ± 6	24 ± 6	0.329		
Creatinine (mg/dL)	0.9 (0.6-1.3)	0.8 (0.6 - 1.1)	1.2(0.7 - 1.8)	<0.001	2.119(1.630-2.755)	<0.001
Sodium (mmol/L)	141 ± 6	142 ± 6	140 ± 8	0.082		
< **Microbial positivity, n (%)**	17 (9.8)	5 (4.5)	12 (19.4)	0.003	3.280 (1.742-6.175)	<0.001
& **Blood product requirement**						
Packed Red Cells (units)	8 (4-12)	8 (4-11)	8 (5-12)	0.488		
Fresh Frozen Plasma (units)	5 (3-8)	4 (2-8)	6 (3-9)	0.035	1.064(1.015-1.115)	0.010
Platelets (units)	2 (1-4)	2 (1-3)	3 (1-4)	0.031	1.064(1.011-1.121)	0.017
@ **Organ failures, n (%)**						
Liver	18 (10.3)	6 (5.4)	12 (19.4)	0.004	2.378 (1.271-4.485)	0.007
Renal	26(14.9)	4 (3.6)	22 (35.5)	<0.001	5.043(2.977-8.524)	<0.001
Cerebral	27 (15.5)	13 (11.6)	14 (22.6)	0.056	1.732(0.955-3.143)	0.071
Coagulation	25(14.4)	11 (19.8)	14 (22.6)	0.022	2.193(1.209-3.978)	0.010
Circulatory	82(47.2)	45 (40.2)	37 (59.7)	0.014	1.869(1.125-3.105)	0.016
Respiratory	76 (43.6)	42 (37.5)	34 (54.8)	0.027	1.698(1.029-2.800)	0.038
# Mechanical ventilation, n (%)	158 (90.8)	96 (85.7)	62 (100)	0.002	24.448(0.829-721)	0.074
Presence of ACLF, n (%)	119 (68.4)	62 (55.4)	57 (91.9)	<0.001	6.636 (2.658-16.562)	<0.001
ACLF grades				<0.001	2.221(1.698-2.904)	<0.001
No ACLF	55 (31.6)	50 (44.6)	5 (8.1)			
ACLF 1	30 (17.2)	23 (20.5)	7 (11.3)			
ACLF 2	59 (33.9)	32 (28.6)	27 (43.5)			
ACLF 3	30 (17.2)	7 (6.3)	23 (37.1)			
Scores						
Child-Turcotte-Pugh Class				0.004	2.511(1.406-4.484)	0.002
A (5-6)	3 (1.7)	3 (2.7)	0			
B (7-9)	64 (36.8)	50 (44.6)	14 (22.6)			
C (10-15)	107 (61.5)	59 (52.7)	48 (77.4)			
MELD-Na	19(15-25)	17(14-21)	24(18-30)	<0.001	1.107 (1.072-1.143)	<0.001
UKELD	53(49-58)	52 (48 -56)	57 (51 -61)	<0.001	1.091(1.050-1.134)	<0.001
CLIF-C OF	10(9-12)	9 (8-11)	12 (10-13)	<0.001	1.470 (1.307-1.653)	<0.001
TIPSS insertion, n (%)	78 (44.8)	55 (49.1)	23 (37.1)	0.127	0.648 (0.387-1.084)	0.099
^ No of endoscopies prior to inclusion	2 (2-3)	2 (2-3)	2 (2-3)	0.378		
Index OGVB, n (%)	74 (42.5)	40 (35.7)	34 (54.8)	0.015	1.397(1.087-1.794)	0.009
NSBB use prior to current episode of	56 (32.2)	45 (40.2)	11 (17.7)	0.002	0.430(0.224-0.825)	0.011

OGVB, n (%)						
@@ **Ongoing alcohol use, n (%)**	99 (56.9)	68 (60.7)	31 (50.0)	0.172		
$$ **ACLF prior to current episode of OGVB, n (%)**	28 (16.1)	5 (4.5)	23 (37.1)	<0.001	4.382 (2.605-7.369)	<0.001
Length of stay						
Length of stay in ICU (days)	6 (2-11)	5 (2-10)	8 (2-12)	0.207		
Length of stay in hospital (days)	14 (8-22)	15 (7-29)	13 (8-17)	0.050		

*Following resuscitation on day of ICU admission

< Microbial positivity of samples collected within first 48 hours of admission including positive cultures of the blood, urine and sputum or a diagnosis of spontaneous bacterial peritonitis.

& From the time of presentation with OGVB till discharge from ICU or death which-ever is earlier.

@ Organ failures were defined based on method described by Moreau et al. (1)

Mechanical ventilation done within 24 hours of OGVB for either for respiratory failure, high grade hepatic encephalopathy, air-way protection or a combination of these factors.

^ This represents the total number endoscopies the patient has had before admission to RFH ICU

@@ ongoing alcohol abuse is defined by alcohol abuse in 3 months preceding OGVB

$$ Presence of ACLF In preceding 2 weeks.

West-Haven criteria was used to categorise hepatic encephalopathy. (2)

Abbreviations: ACLF: Acute on chronic liver failure; AD: Acute decompensation of liver cirrhosis; AIH: Auto-immune hepatitis; ALD: Alcoholic liver disease; CLIF: European Foundation for the study of chronic liver failure; HBV: Hepatitis-B virus; HCV: Hepatitis-C virus; ICU: Intensive care unit; MELD-Na: Model for End-Stage Liver Disease-sodium; NAFLD: Non-alcoholic liver disease; OF: Organ failure; OGVB: Oesophago-gastric variceal bleeding; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; NSBB: Non-selective beta blockers; TIPSS: Transjugular intrahepatic portosystemic shunt: VBL: Variceal band ligation.

Categorical variables are displayed in percent and continuous variables as mean ± SD (for Normally distributed data) or median (IQR) (Nonparametric testing for skewed data). Chi-square test was used for categorical variables, paired t-test for Normally distributed continuous variable and Mann-Whitney U test was used for Non-parametric testing.

Table 3: *Multivariate analysis of factors determining 42-day mortality in the whole patient cohort

Variable	All patients (N= 174)	Survivors N=112 (64.4 %)	Non-Survivors N=62 (35.6 %)	P-value	Univariate Cox-regression		Multivariate Cox-regression Model 1		Multivariate Cox-regression Model 2		Multivariate Cox-regression Model 3	
					HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (years)	51.5 ± 11.7	50.1± 11.4	53.7 ±12.3	0.048	1.023 (1.002-1.045)	0.033	1.032(1.007 - 1.058)	0.012	1.026 (1.002 - 1.051)	0.035	1.023(1.003-1.051)	0.026
White cell count (WCC) ($x10^6$/L)	9.0 (6.3-12.4)	8.1 (5.8 - 11.0)	11.8 (8.0 - 17.5)	<0.001	1.086 (1.046-1.128)	<0.001	1.047(1.005-1.090)	0.027	1.056(1.017-1.097)	0.006	1.046(1.004-1.090)	0.033
< Microbial positivity, n (%)	17 (9.8)	5 (4.5)	12 (19.4)	0.003	3.280 (1.742-6.175)	<0.001	2.512(1.278-4.941)	0.008	2.906 (1.518-5.561)	0.014	-	-
Fresh Frozen Plasma (units)	5 (3-8)	4 (2-8)	6 (3-9)	0.035	1.064(1.015-1.115)	0.010	1.049(0.977-1.127)	0.185	1.054(0.986-1.127)	0.088	-	-
Platelets (units)	2 (1-4)	2 (1-3)	3 (1-4)	0.031	1.064(1.011-1.121)	0.017	0.950(0.883-1.022)	0.166	1.005(0.937-1.078)	0.956	-	-
ACLF prior to current episode of OGVB, n (%)	28 (16.1)	5 (4.5)	23 (37.1)	<0.001	4.382 (2.605-7.369)	<0.001	1.329(0.850-2.080)	0.174	-	-	1.977(0.997-3.920)	0.051
CLIF-C OF score	10(9-12)	9 (8-11)	12 (10-13)	<0.001	1.470 (1.307-1.653)	<0.001	1.318(1.120-1.550)	0.001	-	-	1.289(1.102-1.508)	0.001
ACLF, Yes (%)	119 (68.4)	62 (55.4)	57 (91.9)	<0.001	6.636 (2.658-16.562)	<0.001			4.580 (1.800-11.653)	0.001		

*Cox proportional hazards regression model was used for the analysis

< Microbial positivity of samples collected within first 48 hours of admission including positive cultures of the blood, urine and sputum or a diagnosis of spontaneous bacterial peritonitis.

Abbreviations: ACLF: Acute on chronic liver failure; CI: Confidence interval: HR: Hazard ratio; OGVB: Oesophago-gastric variceal bleeding.

Table 4: *Multivariate analysis of factors determining 1-Year mortality in the whole patient cohort.

Variable	All patients (N= 174)	Survivors (n=94, (54%))	Non-Survivors (n=80, (46%))	P-value	Univariate Cox-regression		*Multivariate Cox-regression Model 1		*Multivariate Cox-regression Model 2		*Multivariate Cox-regression Model 3	
					HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (years)	51.45 ± 11.7	49.44 ± 11.06	53.81 ±12.1	0.014	1.027 (1.007-1.046)	0.007	1.034 (1.013-1.056)	0.001	1.030(1.009-1.052)	0.004	1.034(1.013-1.056)	0.002
White cell count (WCC) ($x10^6$/L)	9.0 (6.3-12.4)	8.2 (5.5 - 11.2)	10.7 (7.3 - 15.4)	<0.001	1.070 (1.033-1.108)	<0.001	1.030(0.992-1.069)	0.125	1.044(1.008-1.081)	0.017	1.032(0.994-1.071)	0.101
< Microbial positivity, n (%)	17 (9.8)	5 (2.9)	12 (15)	0.032	2.571(1.388-4.761)	0.003	1.962(1.029-3.740)	0.041	2.301(1.224-4.324)	0.010	-	-
Fresh Frozen Plasma (units)	5 (2.75-8)	4 (2-8)	6 (3-8)	0.028	1.054(1.009-1.101)	0.018	1.007(0.958-1.057)	0.791	1.053(1.006-1.103)	0.026	-	-
ACLF prior to current episode of OGVB, n (%)	28 (16.1)	0 (0)	28 (35.0)	<0.001	5.333 (3.293 - 8.636)	<0.001	2.218 (1.180-4.169)	0.013	-	-	2.462(1.326-4.571)	0.004
CLIF-C OF score	10 (9-12)	9 (8-10)	11.5 (10-13)	<0.001	1.483 (1.334-1.648)	<0.001	1.305 (1.133-1.503)	<0.001	-	-	1.304(1.139-1.492)	<0.001
ACLF, yes (%)									5.174(2.350-11.390)	<0.001		

*Cox proportional hazards regression model was used for the analysis.
< Microbial positivity of samples collected within first 48 hours of admission including positive cultures of the blood, urine and sputum or a diagnosis of spontaneous bacterial peritonitis.
Abbreviations: ACLF: Acute on chronic liver failure; CI: Confidence interval: CLIF: European Foundation for the study of chronic liver failure; HR: Hazard ratio: OF: Organ failure; OGVB: Oesophago-gastric variceal bleeding.

Table 5: *Multivariate analysis of factors determining 42-day mortality in the subgroup of patients with acute on chronic liver failure

Variable	All patients with ACLF (n= 119)	Survivors (n=62 (52.1%))	Non-Survivors (n=57 (47.9%))	P value	Univariate Cox-Regression		*Multivariate Cox-regression Model 1		*Multivariate Cox-regression Model 2	
					HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (years)	52.9 ± 11.3	51 ± 10.8	55.1 ± 11.5	0.045	1.027(1.003-1.050)	0.025	1.036(1.011-1.062)	0.005	1.032(1.008-1.057)	0.010
White cell count (WCC) ($x10^6$/L)	9.5 (6.5 - 13.5)	8.7 (6.0-11.6)	10.9 (7.8 -17)	0.003	1.048(1.008-1.091)	0.020	1.023 (0.979-1.070)	0.314	1.016(0.974-1.061)	0.462
CLIF-C OF	11 (10-12)	11 (10 - 11.25)	12 (11-13)	<0.0001	1.379(1.185-1.605)	<0.001	1.226 (1.010-1.488)	0.039	1.377(1.176-1.612)	<0.001
TIPSS insertion, n (%)	57 (47.9)	37 (58.5)	20 (35.2)	0.012	2.157(1.251-3.718)	0.006	0.540(0.309-0.943)	0.030	0.511(0.292-0.896)	0.019
ACLF prior to current episode of OGVB, n (%)	28 (23.5)	5 (8)	23 (40.4)	<0.001	2.938(1.724-5.007)	<0.001	2.049 (1.030-4.074)	0.041	-	-

*Cox proportional hazards regression model was used for the analysis
Abbreviations: ACLF: Acute on chronic liver failure; CI: Confidence interval: CLIF: European Foundation for the study of chronic liver failure; HR: Hazard ratio: OF: Organ failure; OGVB: Oesophago-gastric variceal bleeding; TIPSS: Transjugular intrahepatic portosystemic shunt.

Table 6. * Difference in characteristics of patients undergoing TIPSS Vs. No TIPSS (All Patients)

Variable	All patients (N= 174)	TIPSS (n= 78 (44.8%))	No TIPSS (n= 96 (55.2%))	P-value
Age (years)	51.5 ± 11.7	50.18 ± 10.27	52.48 ± 12.75	0.199
Male gender, n (%)	134 (77)	59 (75.6)	75 (78.1)	0.699
Etiology of cirrhosis, n (%)				0.056
Alcohol	106 (60.9)	57 (73.1)	49 (51.0)	
HBV	3 (1.7)	1(1.3)	2(2.1)	
HCV	10 (5.7)	2 (2.6)	8 (8.3)	
NAFLD	7 (4)	2(2.6)	5(5.2)	
PBC/PSC/AIH	13 (6.9)	4(5.1)	9(9.4)	
Cryptogenic	7 (4)	1 (1.3)	6 (6.3)	
Viral + ALD	19 (10.9)	9 (11.5)	10 (10.4)	
Other	9 (5.2)	2 (2.6)	7 (7.3)	
Clinical features at Presentation, n (%)				
Ascites				0.514
None	59 (33.9)	23 (29.5)	36 (37.5)	
Mild-Moderate	54 (31)	25 (32.1)	29 (30.2)	
Severe	61 (35.1)	30 (38.5)	31 (32.3)	
Hepatic Encephalopathy, n (%)				0.076
None	51 (29.3)	17 (21.8)	34 (35.4)	
Grade 1/2	96 (55.2)	45 (57.7)	51 (53.1)	
Grade 3/4	27 (15.5)	16 (20.5)	11 (15.5)	
Clinical parameters at Presentation				
Temperature (^{o}C)	36.5 (36 - 37.1)	36.5 (35.9 -37.1)	36.5(36.0-37.1)	0.942
Mean Arterial Pressure (mmHg)	77 (70 - 87)	80 (70-87)	77 (68-86)	0.278
Respiratory Rate (/min)	14 (12-16)	14 (12-16)	14 (12-16)	0.973
P/F Ratio (PaO2/Fi02 ratio)	231 (142-316)	208(133-297)	231 (142-313)	0.704
Heart Rate (HR) (/min)	91 ± 18	91 ± 17	90 ± 18	0.794
Laboratory values				
Haemoglobin (g/dl)	8.9 ± 1.7	8.9 ± 1.5	8.9 ± 1.8	0.999
Platelet Count (x10^{9}/L)	68 (47-93)	68 (47 -91)	68 (47-107)	0.306
White Blood Cells (WBC) (x10^{6}/L)	9.0(6.3-12.4)	9.3 (6-12.5)	8.7 (6.6-12.4)	0.893
International Normalised Ratio (INR)	1.6(1.4-2.0)	1.6 (1.4-2.0)	1.7 (1.4 -2.1)	0.944
Total Bilirubin (mg/dl)	3.6 (1.7-6.7)	3.0 (1.6-6.0)	4.0 (1.8 - 8.2)	0.064
Albumin (g/dL)	24 ± 6	23 ± 6	25 ± 6	0.023
Creatinine (mg/dL)	0.9 (0.6-1.3)	0.8 (0.6 - 1.2)	0.9 (0.7-1.4)	0.048
Sodium (mmol/L)	141.1 ± 6.4	141.4 ± 6.9	141 ± 5.9	0.636
< **Microbial positivity, n (%)**	17 (9.8)	8 (10.3)	9 (9.4)	0..960
& **Blood Product Requirement**				
Packed Red Cells (units)	8 (4-12)	10 (6-12)	7(3-10)	0.001
Fresh Frozen Plasma (units)	5(2.75-8)	5 (3-8)	5(2-8)	0.029
Platelets (units)	2 (1-4)	2 (1-4)	2(1-3)	0.065
@ **Organ failures, n (%)**				
Liver	18 (10.3)	5 (6.4)	13 (13.5)	0.125
Renal	26(14.9)	10 (12.8)	16 (16.7)	0.479
Cerebral	27 (15.5)	16 (20.5)	11 (11.5)	0.101

Coagulation	25(14.4)	9(11.5)	16 (16.7)	0.338
Circulatory	82(47.2)	40(51.3)	42 (43.8)	0.322
Respiratory	76(43.6)	34 (43.6)	42 (43.8)	0.983
# Mechanical ventilation, n (%)	158 (90.8)	73 (93.6)	85 (88.5)	0.252
ACLF Grades				0.562
No ACLF	55 (31.6)	21 (26.9)	34 (35.4)	
ACLF 1	30 (17.2)	16 (20.5)	14 (14.6)	
ACLF 2	59 (33.9)	28 (35.9)	31 (32.3)	
ACLF 3	30 (17.2)	13 (16.7)	17 (17.2)	
Scores				
Child-Turcotte- Pugh Class				0.227
A (5-6)	3 (1.7)	0 (0.0)	3 (3.1)	
B (7-9)	64 (36.8)	27 (34.6)	37 (38.5)	
C (10-15)	107 (61.5)	51 (65.3)	56 (58.3)	
MELD-Na	19 (15-25)	18 (15-23)	20 (15-27)	0.157
UKELD	53 (49-58)	53 (48-57)	54 (50-58)	0.217
CLIF-C OF	10 (9-12)	10 (9-11)	10 (8-12)	0.577
No ACLF	55 (31.6)	21 (26.9)	34 (35.4)	0.231
Yes ACLF	119 (68.4)	57 (73.1)	62 (64.6)	
^ No of endoscopies prior to Inclusion	2 (2-3)	2(2-3)	2 (2-3)	0.106
Index OGVB, n (%)	74 (42.5)	28 (35.9)	46 (47.9)	0.111
NSBB use prior to current episode of OGVB, n (%)	56 (32.2)	21 (26.9)	35 (36.5)	0.181
$$ **ACLF prior to current episode of OGVB (%)**	28 (16.1)	9 (11.5)	19 (10.9)	0.141
Survival data				
28-day Mortality, n (%)	59 (33.9)	22 (28.2)	37 (38.5)	0.152
42-day Mortality, n (%)	62 (35.6)	23 (29.5)	39 (40.6)	0.127
3-months mortality, n (%)	72 (41.4)	25 (32.1)	47 (49)	0.038
1-year mortality, n (%)	80 (45.9)	30 (38.5)	50 (52.1)	0.073
ICU Survival, (alive, n, %)	131 (75.3)	60 (76.9)	71 (74)	0.652
Hospital Survival (alive, n, %)	114 (65.5)	55 (70.5)	61 (63.5)	0.332

*Following resuscitation on day of ICU admission
< Microbial positivity of samples collected within first 48 hours of admission including positive cultures of the blood, urine and sputum or a diagnosis of spontaneous bacterial peritonitis.
& From the time of presentation with OGVB till discharge from ICU or death which-ever is earlier.
@ Organ failures were defined based on method described by Moreau et al. (1)
**To maintain mean arterial pressure >70 mm Hg
Mechanical ventilation done within 24 hours of OGVB for either for respiratory failure, high grade hepatic encephalopathy, air-way protection or a combination of these factors.
$ Renal replacement therapy instituted within 24 hours of OGVB
^ This represents the total number endoscopies the patient has had before admission to RFH ICU
@@ ongoing alcohol abuse is defined by alcohol abuse in 3 months preceding OGVB
$$ Presence of ACLF In preceding 2 weeks.
West-Haven criteria was used to categorise hepatic encephalopathy. (2)
Abbreviations: ACLF: Acute on chronic liver failure; AD: Acute decompensation of liver cirrhosis; AIH: Auto-immune hepatitis; ALD: Alcoholic liver disease; CLIF: European Foundation for the study of chronic liver failure; HBV: Hepatitis-B virus; HCV: Hepatitis-C virus; ICU: Intensive care unit; MELD-Na: Model for End-Stage Liver Disease-sodium; NAFLD: Non-alcoholic liver disease; OF: Organ failure; OGVB: Oesophago-gastric variceal bleeding; PBC: Primary biliary cirrhosis; PSC:

Primary sclerosing cholangitis; NSBB: Non-selective beta blockers; TIPSS: Transjugular intrahepatic portosystemic shunt; VBL: Variceal band ligation.
Categorical variables are displayed in percent and continuous variables as mean ± SD (for Normally distributed data) or median (IQR) (Nonparametric testing for skewed data). Chi-square test was used for categorical variables, paired t-test for Normally distributed continuous variable and Mann-Whitney U test was used for Non-parametric testing.