Published in final edited form as:

Hepatology. 2019 May ; 69(5): 2150–2163. doi:10.1002/hep.30494.

Incidence and Mortality of Acute on Chronic Liver Failure using Two Definitions in Patients with Compensated Cirrhosis

Nadim Mahmud¹, David E. Kaplan^{1,2}, Tamar H. Taddei^{3,4}, and David S. Goldberg^{1,5}

¹Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

²Department of Medicine, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA

³Division of Digestive Diseases, Yale University School of Medicine, New Haven, CT

⁴VA Connecticut Healthcare System, West Haven, CT

⁵Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Abstract

Background and Aims: The term acute on chronic liver failure (ACLF) intends to identify chronic liver disease patients who develop rapid deterioration of liver function and high short-term mortality after an acute insult. The two prominent definitions (European Association for the Study of the Liver [EASL] and Asian Pacific Association for the Study of the Liver [APASL]) differ, and existing literature applies to narrow patient groups. We sought to compare ACLF incidence and mortality among a diverse cohort of compensated cirrhotic patients, using both definitions.

Methods: Retrospective cohort study of incident compensated cirrhotic patients in the Veterans Health Administration from 2008–2016. First ACLF events were identified for each definition. Incidence rates were computed as events per 1,000 person-years, and mortality was calculated at 28 and 90 days.

Results: Among 80,383 cirrhotics with 3.35 years median follow-up, 783 developed EASL and APASL ACLF, 4,296 EASL alone, and 574 APASL alone. The incidence rate of APASL ACLF was 5.7 per 1,000 person-years (95% CI 5.4 – 6.0), and EASL ACLF was 20.1 (95% CI 19.5 – 20.6). The 28- and 90-day mortalities for APASL ACLF were 41.9% and 56.1%, respectively, and for EASL ACLF were 37.6% and 50.4%. The median bilirubin at diagnosis of EASL-alone ACLF was 2.0mg/dL (IQR 1.1–4.0). Patients with hepatitis C or non-alcoholic fatty liver disease had among the lowest ACLF incidence rates, but the highest short-term mortality.

Conclusion: There is significant discordance in ACLF events by EASL and APASL criteria. The majority of patients with EASL-alone ACLF have preserved liver function, suggesting the need for more liver-specific ACLF criteria.

Corresponding Author Contact Information: Nadim Mahmud, 3400 Civic Center Blvd, 4th Floor, South Pavilion, Philadelphia, PA 19104, USA., Tel.: +1 215-349-8222; Fax: +1 215-349-5915, nadim.mahmud@uphs.upenn.edu.

Author Disclosures

We confirm that none of the authors have any conflicts of interest or other relevant disclosures pertaining to this manuscript.

Keywords

European Association for the Study of the Liver (EASL); Asian Pacific Association for the Study of the Liver (APASL); Veterans Health Administration (VHA); criteria; compensated cirrhosis

Acute on chronic liver failure (ACLF) has been defined as a clinical syndrome where an acute insult in a patient with chronic liver disease leads to rapid deterioration of liver function associated with extremely high short-term mortality. ACLF is distinct from acute liver failure, which by definition requires underlying normal hepatic function. It is also distinct from progressive cirrhosis, which typically results in stepwise decline and eventual decompensation. In contrast to decompensated cirrhosis, which carries a two-year median survival of ~2 years,^{1, 2} patients with ACLF have 90-day mortality in excess of 50%.³⁻⁶ Given the grave prognosis of ACLF, there is significant interest in identifying risk factors and improved prognostic models for ACLF in order to identify patients who may require higher levels of care, enrollment in trials testing advanced liver support devices, and/or urgent liver transplant evaluation.

However, controversy persists regarding the appropriate diagnostic criteria for ACLF. More than a dozen proposed definitions of ACLF exist, all of which vary in scope and prognostic value.⁷ The two seminal, consensus-based, and most widely accepted definitions are the Asian Pacific Association for the Study of the Liver (APASL) criteria and the European Association for the Study of the Liver (EASL) criteria. APASL defines ACLF as “an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (international normalized ratio [INR] ≥ 1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, that is associated with a high 28-day mortality.”⁵ In contrast, the EASL definition requires an acute decompensation (hepatic encephalopathy, gastrointestinal bleeding, ascites, or bacterial infection) followed by the development of one or more organ failures to assign severity grades of ACLF.⁴

Beyond the ongoing debates surrounding ACLF definitions,⁸⁻¹⁰ several critical knowledge gaps remain. First, epidemiologic data on ACLF are sorely lacking. The combined EASL and APASL cohorts comprise fewer than 2,000 ACLF patients, and are based largely on patients treated at tertiary care centers.¹¹ Second, the available data do not reflect diverse etiologies of cirrhosis. The APASL definition was derived from a cohort of predominantly hepatitis B-infected patients, while nearly 60% of the EASL ACLF cohort had alcohol-induced liver disease. There are limited data from North America,¹² and no studies to date have included large cohorts of patients with cirrhosis from fatty liver disease or hepatitis C. Finally, the performance and utility of major competing ACLF definitions have not been directly compared in the same cohort, leaving the literature and standards for future research in a state of ongoing confusion.

As such, we sought to determine the incidence and mortality of ACLF among a broad cohort of patients with compensated cirrhosis and to compare them using the consensus-recommended APASL and EASL ACLF criteria.

Experimental Procedures

Study Design and Cohort Creation

We performed a retrospective cohort study using data from the Veterans Health Administration (VHA), specifically focused on Veterans whose data had been collected as part of the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) study group. This database was selected because the VHA is the largest single provider of liver care in the United States (US), and is the largest nationally-representative dataset of patients with chronic liver disease including inpatient and outpatient clinical, laboratory, and prescription data. The VOCAL cohort has also been used for numerous prior studies focused on patients with chronic liver disease,^{13–16} and is very representative of the United Network for Organ Sharing (UNOS) liver transplant distribution from an etiology standpoint (Supplemental Figure 1).¹⁷ The derivation of the VOCAL dataset has been previously described,¹⁸ but in brief, the VHA relational database contains a range of detailed demographic, clinical, laboratory, imaging, pharmacy, admissions, financial, and administrative coding data. For this study, nearly ~129,000 patients with incident cirrhosis were identified in the VHA system between 2008 and 2016 using a validated algorithm with one inpatient or two outpatient International Classification of Disease (ICD)-9 cirrhosis codes (571.2 or 571.5) or adapted ICD-10 codes.¹⁹ Mortality data was obtained from the Vital Status File, and transplantation outcomes were cross-referenced from the UNOS Standard Transplant Analysis and Research (STAR) data file. For each patient, a six-month baseline period from the time of cirrhosis diagnosis was established over which selection criteria were applied. We included patients aged ≥ 18 years who were actively engaged in care within the VHA, defined as completion of two or more outpatient visits, consistent with prior methods.^{16, 20, 21} We excluded patients with decompensated cirrhosis who by definition cannot be classified as having ACLF per the APASL criteria, using a validated algorithm that includes one inpatient or two outpatient ICD-9/ICD-10 codes for ascites, bleeding esophageal varices, or hepatic encephalopathy.²² Based on the bilirubin criteria for APASL ACLF, patients were also excluded if they had a baseline total bilirubin ≥ 5mg/dL (with at least two values checked in the baseline period). Finally, patients were excluded if they died within the baseline period, received liver transplantation prior to or within the baseline period, or did not have follow-up data beyond the baseline period.

Variable Collection

The VHA relational database was queried to obtain detailed demographic (age, sex, race), clinical (body mass index [BMI]), laboratory (liver-associated enzymes, coagulation, and renal function parameters), and comorbidity data (hypertension, diabetes, coronary artery disease, congestive heart failure, cerebrovascular accident, atrial fibrillation, pulmonary embolism, and hepatocellular carcinoma). Inpatient admissions data, medication administration data, ICD-9 codes, and current procedure terminology (CPT) codes were also obtained for all patients to facilitate subsequent outcomes ascertainment (detailed below). Etiology of liver disease was determined using an algorithm validated in the VHA dataset by Beste et al,²³ with subsequent six-level categorization (hepatitis C [HCV], hepatitis B [HBV], alcoholic liver disease [EtOH], HCV + EtOH, non-alcoholic fatty liver disease [NAFLD], and other).

Ascertainment of APASL ACLF Events

In accordance with the APASL consensus definition of ACLF,⁵ patients in the analytic cohort were screened for events with a total bilirubin ≥ 5 mg/dL and INR ≥ 1.5 complicated within 28 days by either ascites and/or hepatic encephalopathy. We constructed an algorithm to search for lab criteria values occurring within 7 days of each other, followed by development of ascites or hepatic encephalopathy. These decompensations were identified based on validated ICD-9 algorithms (Supplemental Table 1).²² Of note, if a patient received warfarin within 3 days or rivaroxaban within 1 day prior to an elevated INR, this instance was not considered to meet APASL INR criteria. Structured query language (SQL) followed by manual validation was used to identify administration and timing of warfarin or rivaroxaban from the relational database (Supplemental Table 2). Given expected discordance between the timing of ICD-9 coding relative to actual onset of hepatic decompensation, a sensitivity analysis extending the search window for ascites or hepatic encephalopathy events to 56 days was performed.

Ascertainment of EASL ACLF Events

The EASL definition of ACLF refers to inpatient admissions with an acute decompensation (hepatic encephalopathy, gastrointestinal [GI] bleeding, ascites, or bacterial infection) that is complicated by organ failures (OFs) within 28 days that are defined according to the EASL Chronic Liver Failure Consortium (CLIF-C) scoring system.⁴ There are six potential organ failures—liver, kidney, brain, coagulation, circulation, and respiratory—and based on the number and types of OFs present a patient is scored from EASL ACLF grade 0 (no ACLF) to grade 3 (severe ACLF).

Inpatient admissions with acute decompensations were identified through a combination of adapted validated algorithms,^{22, 24–28} ICD-9 codes, CPT codes, and pharmacy administration data (Supplemental Table 3). The first 28 days of each admission were searched for specific OFs, which were ascertained in accordance with EASL criteria. Liver failure was defined as total bilirubin >12 mg/dL, and coagulation failure was defined as INR ≥ 2.5 . If a patient had received warfarin within 3 days or rivaroxaban within 1 day prior to the elevated INR value, this was not considered to meet EASL-CLIF coagulation failure. The definition of kidney failure involved two severity classes (as per EASL) and accounted for baseline chronic kidney disease using consensus Kidney Disease: Improving Global Outcomes (KDIGO) criteria, where different creatinine changes from baseline were required for patients with normal baseline kidney function versus those with chronic kidney disease (Supplemental Table 4).²⁹ Given the lack of granular PaO₂ and FiO₂ data (upon which the EASL OF is based), respiratory failure was defined as the presence of mechanical ventilation. Previously validated approaches were adapted to identify these events (Supplemental Table 5).^{30, 31} Brain OF required a combination of ICD-9 codes for hepatic encephalopathy, identified through a validated algorithm,²² plus administration of lactulose or rifaximin (Supplemental Table 6). Finally, circulatory failure was defined by the administration of vasopressors, which were identified through a combination of SQL database queries and subsequent processing (Supplemental Table 7). The number and types of OFs present over the 28-day window were then used to classify EASL ACLF events into severity grades 0, 1, 2, or 3 in accordance with published criteria.^{3, 4} A sensitivity analysis

extending the OF search window to the entire admission duration (for those >28 days in duration) was also performed.

Descriptive Analysis

Patient demographic, laboratory, and clinical characteristics were compared among patients with no ACLF events, APASL ACLF alone, EASL ACLF alone, and EASL + APASL ACLF. Medians and interquartile ranges were presented for continuous variables. Wilcoxon rank-sum and chi-squared tests were performed for continuous and categorical variables, respectively, with a two-tailed $\alpha = 0.05$ maintained as the threshold for statistical significance. STATA 14.2/IC was used for data management for this and all subsequent analyses.

Primary Analysis

The incidence rates of first ACLF events were computed from the end of the baseline period to the point of maximum follow-up, accounting for death and transplant events. Incidence rates were presented as ACLF events per 1,000 person-years with 95% confidence intervals. Short-term mortality was computed at 28 and 90 days from the onset of ACLF events. APASL ACLF events were considered to ‘start’ at the first time-point when all criteria were met. EASL ACLF events ‘started’ at the time of the last OF identified within the 28-day window from inpatient admission. Incidence rates and mortality were computed separately for APASL ACLF, EASL ACLF events overall, and EASL ACLF by grade. EASL ACLF incidence rates were further stratified by category of acute decompensation. For both APASL and EASL ACLF, incidence rates and mortality were also computed for each etiology of liver disease. Associated Kaplan-Meier failure curves (for ACLF incidence) and survival curves (for ACLF mortality) were produced, with log-rank tests performed to compare the overall distributions. Finally, as a comparator, the short-term mortality associated with any non-EASL ACLF inpatient admissions was computed, both overall and stratified by diagnosis of acute decompensation.

Secondary Analyses

Laboratory parameters at the time of ACLF events as well as at the time of death were compared among patients with APASL ACLF alone, EASL ACLF alone, and ACLF by both EASL + APASL criteria. Among patients with EASL ACLF, the distribution of OFs and acute decompensations were compared for different severity grades using bar graphs. In patients with grade 3 ACLF, OFs were also compared by etiology of liver disease. Bar graphs were then produced to evaluate type of infectious etiology (bacteremia, skin and soft tissue infection/musculoskeletal [SST/MSK], spontaneous bacterial peritonitis [SBP], pneumonia, or other) and origin of GI bleed (peptic ulcer-related upper, non-ulcer related upper, lower, small bowel, or not otherwise specified [NOS]) by EASL ACLF grade. These distributions were also compared by etiology of liver disease. Finally, as an exploratory analysis to evaluate the impact of liver-specific injury in EASL ACLF, short-term mortalities were computed for events stratified by total bilirubin greater ≥ 5 mg/dL and <5 mg/dL.

Results

ACLF Events and Patient Characteristics

After application of inclusion and exclusion criteria, a total 80,383 patients with incident cirrhosis were included in the analytic cohort (Supplemental Figure 2). Of these patients, 783 developed clinical events that met definitions for ACLF by both EASL and APASL criteria over a median follow-up time of 3.35 years (IQR 1.73, 5.69), while 4,296 developed events qualifying for ACLF by EASL criteria alone, 574 developed events meeting APASL ACLF criteria alone, and 74,730 never experienced ACLF. Patients in these categories differed across a range of demographic and clinical parameters (Table 1). Overall, patients who developed an EASL-alone ACLF event were more similar to those who did not develop ACLF, in terms of age, baseline cirrhosis severity, and comorbidities. Patients with EASL + APASL or APASL-alone ACLF events tended to be sicker at baseline (median model for end-stage liver disease [MELD]-Na 11.0 versus 9.0 EASL-alone ACLF; $p < 0.001$), younger (mostly age 40–65 years), and less likely to have cardiovascular comorbidities or chronic kidney disease as compared to those with EASL ACLF alone or no ACLF.

A sensitivity analysis extending the search window for decompensation to 56 days classified an additional 61 patients as meeting criteria for APASL ACLF, less than a 5% difference in outcome ascertainment. For EASL ACLF, a sensitivity analysis extending the search window for OFs to the entire admission classified 30 additional patients with ACLF, less than a 1% difference in outcome ascertainment. The overall proportion of ACLF outcomes reclassification with both sensitivity analyses applied was less than 0.2% (Supplemental Table 8).

Incidence and Mortality of ACLF

The incidence rates per 1,000 patient-years as well as the short-term mortalities of ACLF events are shown in Table 2. The observed incidence rates and mortality of APASL ACLF events fell between those of grade 2 and grade 3 EASL ACLF. Overall, the highest short-term mortality was observed in patients with grade 3 EASL ACLF (28-day 74.3%, 90-day 83.4%) while the lowest was in grade 1 EASL ACLF (28-day 19.3%, 90-day 32.5%), and survival declined with increasing EASL ACLF grade (Supplemental Figure 3; $p < 0.001$). As a comparator, the short-term mortality rates of any non-ACLF inpatient admission were 5.0% at 28 days and 12.1% at 90 days. Grade 3 EASL ACLF was more likely to be provoked by infection (incidence rate 2.6, 95% CI: 2.4–2.8) as compared to ascites (0.9, 95% CI: 0.8–1.0), GI bleed (0.8, 95% CI: 0.7–1.0), or hepatic encephalopathy (1.5, 95% CI: 1.4–1.7). Finally, the short-term mortalities for patients with EASL + APASL ACLF were higher than EASL or APASL alone (Supplemental Table 9).

When stratified by etiology of liver disease, patients with hepatitis C or NAFLD had among the lowest incidence rates of ACLF, but had the highest short-term mortalities (Table 3). In contrast, patients with EtOH or HCV + EtOH had the highest incidences of ACLF, but generally lower short-term mortalities. This was true for both APASL and EASL ACLF definitions (Figures 1 and 2; all $p < 0.001$).

Laboratory Profiles of ACLF Events

At the time of ACLF events, patients with EASL + APASL ACLF had higher median transaminases, total bilirubin, and INR as compared to those with EASL or APASL ACLF alone (Table 4). Patients with EASL ACLF alone had the lowest median aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and INR values among all groups, and the highest serum creatinine. Among patients who died, those with EASL ACLF had significantly lower AST, ALT, and total bilirubin values immediately prior to death as compared to patients with EASL + APASL or APASL ACLF alone (Supplemental Table 10; all $p < 0.001$).

Characteristics of EASL ACLF Events

In all grades of EASL ACLF, kidney failure was the most commonly observed OF (Figure 3A). In grade 3 EASL ACLF, this was followed by circulatory failure and coagulation failure. In grade 1 EASL ACLF, circulatory, coagulation, respiratory, and liver OF were uncommon. Overall, the least commonly observed OF was liver failure. Infection was the most commonly observed precipitant of EASL ACLF in grades 1 and 3, while hepatic encephalopathy was the most common in grade 2 EASL ACLF (Figure 3B). Among those with grade 3 ACLF, HCV and NAFLD patients had the highest proportions of circulatory failure (Figure 3C), and a higher proportion of infection as compared to HBV, EtOH, or HCV + EtOH patients. Bacteremia and non-ulcer related upper GI bleeding were increasingly likely infectious and GI bleeding precipitants, respectively, for increasing EASL ACLF grades (Supplemental Figure 4A–B). These ACLF precipitants were also extremely common among all etiologies of liver disease (Supplemental figures 4C–D).

Exploratory Analysis

When stratified by total bilirubin $< 5 \text{ mg/dL}$ or $\geq 5 \text{ mg/dL}$ during EASL ACLF events, the short-term mortalities were uniformly higher for patients with total bilirubin $\geq 5 \text{ mg/dL}$, for each grade and acute decompensation (Supplemental Table 11). For example, the overall EASL ACLF mortalities for patients with total bilirubin $< 5 \text{ mg/dL}$ were 26.4% at 28 days and 39.4% at 90 days, compared to 63.7% and 76.3%, respectively, for those with total bilirubin $\geq 5 \text{ mg/dL}$.

Discussion

In this study of 80,383 patients with incident cirrhosis in the VHA system, we found high incidence and mortality rates of ACLF events by both APASL and EASL definitions. This is the first study of its kind to evaluate a large cohort of cirrhotic patients with diverse etiologies of liver disease, and to compare the two major ACLF definitions. We have clearly demonstrated that the incidence and mortality of ACLF vary greatly based on the criteria used. We also highlight that in a US cohort, the majority of patients with ACLF only meet EASL criteria, and in that setting, have relatively preserved liver function at diagnosis and at death (if applicable). This raises concerns about the validity of the EASL ACLF criteria on two levels: (1) the external validity of the criteria as applied to a broad US population of patients with cirrhosis, and (2) the face/construct validity to classify ACLF as an entity.

The data on ACLF incidence are limited, and primarily come from studies employing the EASL ACLF criteria. In the seminal EASL study, 30.9% of hospitalized patients with cirrhosis had ACLF on presentation or developed it within 28 days.⁴ Of those who did not have ACLF at the time of inpatient admission, 10.8% developed ACLF within 28 days. The only study to address ACLF incidence in outpatients with cirrhosis, from Piano et al, found a 14% probability of ACLF within 12 months among 466 patients.¹¹ Our data demonstrate a ~2% probability of EASL ACLF at one year in a many-fold larger patient sample. There are several likely explanations for this difference. First, the patients in our cohort were less sick at baseline as compared to the Piano et al study (81.1% Child class A versus 54%), and much less sick compared to the seminal EASL cohort, which consisted exclusively of hospitalized patients with cirrhosis. Our cohort was also restricted to patients with compensated cirrhosis, in contrast to both other studies where >65% had experienced prior decompensation. Second, we implemented a novel methodology to adjust for anticoagulation as well as baseline chronic kidney disease to prevent misclassification of non-ACLF events. These adjustments—which are notably absent from published EASL criteria—impact a substantial proportion of patients (10.9% in our cohort), and would otherwise have resulted in these patients inappropriately meeting EASL-CLIF kidney or coagulation OF criteria. Finally, we included only patients with incident cirrhosis in our cohort. It is possible, for example, that there is a time-dependent increase in ACLF incidence with longer durations of cirrhosis.

In comparing both ACLF definitions, we found that while many patients experienced events qualifying as ACLF by both EASL and APASL criteria, there was a significant proportion of patients who were classified as having ACLF by only one set of criteria. For instance, 574 patients met APASL ACLF criteria alone (10.2% of all ACLF patients), and these patients had short-term mortalities similar to grade 2 EASL ACLF. This shows that the EASL definition, despite having much broader criteria for categorizing ACLF, fails to capture a significant proportion of acute events with extremely high short-term mortality. These results highlight ongoing questions as to what an ACLF definition should seek to accomplish. In principle, it should (1) be parsimonious, (2) identify patients with cirrhosis who have a *unique* syndrome that portends high short-term mortality, and (3) identify patients for whom liver-directed therapies might influence outcomes (i.e. transplant or novel emerging therapies). In evaluating APASL ACLF by these standards, it is simple to apply and resembles familiar criteria for acute liver failure. It also identifies patients with high short-term mortality (>50% at 90 days) with events that appear distinct from acute decompensated cirrhosis, as laboratory criteria must be met *before* the diagnosis of ascites or hepatic encephalopathy. Finally, the definition selects for liver-specific injury with criteria based on INR and total bilirubin, although there are no gradations of prognosis at present that might guide patient selection for liver-directed therapies.

In evaluating the EASL ACLF definition by the aforementioned principles, it must first be noted that with respect to clinical practice and research studies, the EASL ACLF definition is more cumbersome and difficult to replicate. Second, EASL ACLF events are not obviously distinct from acute decompensated cirrhosis, as the definition requires precipitating events *prior* to OFs that may include conventional decompensations such as hepatic encephalopathy, SBP, and ascites. Third, because a significant proportion of patients

with EASL ACLF do not have obvious liver injury (bilirubin level <5mg/dl, for example), the face and construct validity of the current EASL ACLF definition are dubious. The inclusion of a large number of patients without obvious liver injury indicates that current EASL ACLF criteria may fail to identify patients most likely to benefit from expedited liver transplantation and/or novel emerging liver therapies. Indeed, the most commonly identified OF in all EASL grades was kidney failure, while liver OF was among the most infrequent. This would suggest that the high short-term mortality in many EASL patients may be attributable to non-hepatotropic insults. These consequences apparently result in part from extremely permissive kidney OF criteria and overly strict liver OF criteria (total bilirubin >12mg/dL). In an exploratory analysis, we found that 'lowering' the total bilirubin threshold to 5mg/dL isolated patients with much higher short-term mortality relative to those with lower total bilirubin values, across all grades of EASL ACLF. This implies that it should be possible to adjust EASL ACLF criteria to identify more patients with high short-term mortality who have liver-specific injury, thus improving the potential utility in allocating liver-directed therapies or recognizing medical futility. Emerging scoring systems aiming to address some of the above concerns, such as the NACSELD-ACLF, are being proposed.³²

Another key finding of this study was that the incidence rates and mortalities of ACLF events—by both EASL and APASL—differ by etiology of liver disease. We found that patients with HCV or NAFLD had the lowest incidence rates of ACLF, but the highest short-term mortality. The reasons for this are unclear, however in our secondary analysis we found that HCV and NAFLD patients with grade 3 ACLF were more likely to have infectious precipitants and more likely to have circulatory failure than any other etiology. This may account for some degree of the high observed mortality in these groups. Separately, there is recent evidence identifying increased BMI as a risk factor for ACLF,³³ and although NAFLD patients had relatively lower incidence of ACLF in this cohort, it is possible that more obese patients have higher mortality from ACLF. Another notable difference in ACLF by etiology of liver disease was that patients with EtOH or HCV + EtOH liver disease had the highest incidence of ACLF, but generally lower short-term mortality as compared to HCV or NAFLD patients. Other authors have speculated that patients in these groups may meet criteria for ACLF on the basis of alcoholic hepatitis.^{34, 35} Indeed, we found that EtOH and HCV + EtOH patients with grade 3 ACLF were less likely to have infectious precipitants, and more likely to have hepatic encephalopathy and ascites as compared to all other etiologies. This would fit with presentations of alcoholic hepatitis, which have a lower short-term mortality in the literature as compared to ACLF more broadly.^{36, 37} The reasons for this are likely multifactorial, including the fact that corticosteroids improve short-term mortality for selected patients with alcoholic hepatitis, and that many do not have cirrhosis. Further research will need to evaluate the impact of treating hepatitis C, weight loss, and alcohol cessation, respectively, on the impact of ACLF incidence and mortality in the above-mentioned cohorts. Stratified analyses of ACLF laboratory results by etiology of liver disease, evaluation of corticosteroid administration, and incorporation of alcohol use assessment tools to better understand the role of alcoholic hepatitis in ACLF is another area of research being pursued by our group.

We acknowledge several limitations in this study. First, there is likely some degree of misclassification of exposures. Although the VHA dataset provides extremely granular

laboratory, pharmacy, and hospitalization data, some coding and ascertainment errors are to be expected. To address this, we used validated algorithms for each variable where able, and performed combined methods of automated and manual validation to ensure data quality. Second, there is likely some misclassification of outcome. Patients with ACLF events outside of the VHA system would not be captured in this dataset. However, our inclusion criteria sought to limit the cohort to patients who are actively engaged in VHA care and would be expected to minimize this issue. Such a misclassification would also be non-differential and bias incidence estimates towards zero for both definitions of ACLF. Third, the criteria for EASL ACLF organ failures could not be perfectly replicated in this study, as PaO₂/FiO₂ data were not available, and West-Haven hepatic encephalopathy grading had to be approximated. However, the methodology employed in this study is more sophisticated than other large database studies that have addressed EASL ACLF, including studies using UNOS data to compute ACLF events at the time of listing.³³ Similarly, assumptions regarding the timing of acute decompensation and OFs for EASL ACLF and the timing of meeting laboratory criteria for APASL ACLF may have impacted the number of patients meeting ACLF criteria. To address this, we performed sensitivity analyses with narrow and expanded ascertainment windows and did not find significant changes in ACLF events. Additionally, the short-term mortalities of EASL ACLF grades and APASL ACLF matched extremely well with the seminal studies.^{4, 5} Finally, there are known external validity limitations related to the VHA dataset. The patients are predominantly male, and have higher proportions of substance abuse and psychiatric comorbidities relative to the general population.^{38, 39} In this study we would not, for example, be able to identify systematic differences in ACLF incidence as a function of sex, and a lack of female patients may skew the distribution of liver disease away from autoimmune etiologies. However, the incidence of cirrhosis is relatively high in this cohort, and is especially enriched with patients who have hepatitis C or fatty liver disease, groups in which ACLF has not been well-studied to date. Furthermore, as transplant is less commonly achieved in VHA patients,⁴⁰ there are far more natural history data available in this cohort.

In conclusion, applying both EASL and APASL ACLF definitions to a broad cohort of patients with cirrhosis revealed extremely high incidence and mortality of ACLF, consistent with prior studies, in addition to notable differences by etiology of liver disease. Further research is clearly needed to elucidate the underlying mechanisms for these observed differences. However, we also found that, simply put, the EASL and APASL criteria do not measure the same entity. The APASL criteria identify high short-term mortality events with liver-specific injury, which is arguably more clinically relevant for providers caring for patients with ACLF, while the EASL criteria widely classify high short-term mortality events from primarily non-hepatotropic causes. There is an urgent need to unify the field around a broadly-applicable, consensus ACLF definition that is liver-specific and makes intuitive sense. Only then can we identify modifiable risk factors for prevention and improve prognostic models once ACLF has developed, thereby allowing for optimized allocation of liver-directed therapies and maximum patient survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

This work was supported by resources and facilities available through the Philadelphia VA Healthcare System as well as the central data repositories maintained by the VA Information Resource Center. The views expressed in this article do not reflect position or policy of the Department of Veterans Affairs or the United States government.

Funding Support

Nadim Mahmud is supported by a National Institutes of Health T32 Research Training Grant (2-T32-DK007740-21A1).

Abbreviations:

ACLF	acute on chronic liver failure
EASL	European Association for the Study of the Liver
APASL	Asian Pacific Association for the Study of the Liver
IQR	interquartile range
INR	international normalized ratio
VHA	Veterans Health Administration
VOCAL	Veterans Outcomes and Costs Associated with Liver Disease
US	United States
ICD	international classification of disease
UNOS	United Network for Organ Sharing
STAR	Standard Transplant Analysis and Research
BMI	body mass index
CPT	current procedure terminology
HCV	hepatitis C
HBV	hepatitis B
EtOH	alcoholic liver disease
NAFLD	non-alcoholic fatty liver disease
SQL	structured query language
GI	gastrointestinal
OF	organ failure
CLIF-C	Chronic Liver Failure Consortium
KDIGO	Kidney Disease: Improving Global Outcomes

SST/MSK	skin and soft tissue/musculoskeletal
SBP	spontaneous bacterial peritonitis
NOS	not otherwise specified
MELD	model for end-stage liver disease
CI	confidence interval
AST	aspartate aminotransferase
ALT	alanine aminotransferase

References

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *Journal of hepatology* 2006;44:217–231. [PubMed: 16298014]
2. Lefton HB, Rosa A, Cohen M. Diagnosis and epidemiology of cirrhosis. *Medical Clinics* 2009;93:787–799. [PubMed: 19577114]
3. Jalan R, Saliba F, Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *Journal of hepatology* 2014;61:1038–1047. [PubMed: 24950482]
4. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–1437.e9. [PubMed: 23474284]
5. Sarin SK, Kedarisetty CK, Abbas Z, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. *Hepatology international* 2014;8:453–471. [PubMed: 26202751]
6. Piano S, Tonon M, Pilutti C, et al. Incidence, predictors and outcomes of acute on chronic liver failure in outpatients with cirrhosis. *Digestive and Liver Disease* 2016;48:e24.
7. Wlodzimirow KA, Eslami S, Abu-Hanna A, et al. A systematic review on prognostic indicators of acute on chronic liver failure and their predictive value for mortality. *Liver International* 2013;33:40–52. [PubMed: 22429562]
8. O'grady J Con: Acute-on-chronic liver failure. *Liver Transplantation* 2017;23:1325–1327. [PubMed: 28650101]
9. Bajaj JS. Defining acute-on-chronic liver failure: will East and West ever meet? *Gastroenterology* 2013;144:1337–1339. [PubMed: 23623966]
10. Singh H, Pai CG. Defining acute-on-chronic liver failure: East, West or Middle ground? *World journal of hepatology* 2015;7:2571. [PubMed: 26557949]
11. Piano S, Tonon M, Vettore E, et al. Incidence, predictors and outcomes of acute-on-chronic liver failure in outpatients with cirrhosis. *Journal of hepatology* 2017;67:1177–1184. [PubMed: 28733221]
12. Bajaj JS, O'leary JG, Reddy KR, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014;60:250–256. [PubMed: 24677131]
13. Goldberg DS, Taddei TH, Serper M, et al. Identifying barriers to hepatocellular carcinoma surveillance in a national sample of patients with cirrhosis. *Hepatology* 2017;65:864–874. [PubMed: 27531119]
14. Serper M, Taddei TH, Mehta R, et al. Association of provider specialty and multidisciplinary care with hepatocellular carcinoma treatment and mortality. *Gastroenterology* 2017;152:1954–1964. [PubMed: 28283421]

15. Mittal S, El-Serag HB, Sada YH, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. *Clinical Gastroenterology and Hepatology* 2016;14:124–131.e1. [PubMed: 26196445]
16. Goldberg DS, French B, Forde KA, et al. Association of distance from a transplant center with access to waitlist placement, receipt of liver transplantation, and survival among US veterans. *Jama* 2014;311:1234–1243. [PubMed: 24668105]
17. Sharing UNfO. National Data. Volume 2018, 2018.
18. Kaplan DE, Dai F, Aytaman A, et al. Development and performance of an algorithm to estimate the Child-Turcotte-Pugh score from a national electronic healthcare database. *Clinical Gastroenterology and Hepatology* 2015;13:2333–2341.e6. [PubMed: 26188137]
19. Goldberg D, Lewis J, Halpern S, et al. Validation of three coding algorithms to identify patients with end-stage liver disease in an administrative database. *Pharmacoepidemiology and drug safety* 2012;21:765–769. [PubMed: 22674685]
20. Gillespie B, Merion R, Ortiz-Rios E, et al. Database comparison of the adult-to-adult living donor liver transplantation cohort study (A2ALL) and the SRTR US Transplant Registry. *American Journal of Transplantation* 2010;10:1621–1633. [PubMed: 20199501]
21. Katz IR, McCarthy JF, Ignacio RV, et al. Suicide among veterans in 16 states, 2005 to 2008: comparisons between utilizers and nonutilizers of Veterans Health Administration (VHA) services based on data from the National Death Index, the National Violent Death Reporting System, and VHA administrative records. *American journal of public health* 2012;102:S105–S110. [PubMed: 22390582]
22. Re VL, Lim JK, Goetz MB, et al. Validity of diagnostic codes and liver-related laboratory abnormalities to identify hepatic decompensation events in the Veterans Aging Cohort Study. *Pharmacoepidemiology and drug safety* 2011;20:689–699. [PubMed: 21626605]
23. Beste LA, Leipertz SL, Green PK, et al. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001–2013. *Gastroenterology* 2015;149:1471–1482.e5. [PubMed: 26255044]
24. Abraham NS, Hartman C, Richardson P, et al. Risk of lower and upper gastrointestinal bleeding, transfusions, and hospitalizations with complex antithrombotic therapy in elderly patients. *Circulation* 2013;
25. Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. *Pharmacoepidemiology and drug safety* 2010;19:596–603. [PubMed: 20140892]
26. Siddique SM, Mehta SJ, Lewis J, et al. Rates of Hospital Readmission Among Medicare Beneficiaries With Gastrointestinal Bleeding Vary Based on Etiology and Comorbidities. *Clinical Gastroenterology and Hepatology* 2018.
27. Schneeweiss S, Robicsek A, Scranton R, et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. *Journal of clinical epidemiology* 2007;60:397–409. [PubMed: 17346615]
28. Patkar NM, Curtis JR, Teng GG, et al. Administrative codes combined with medical records based criteria accurately identified bacterial infections among rheumatoid arthritis patients. *Journal of clinical epidemiology* 2009;62:321–327.e7. [PubMed: 18834713]
29. Kellum JA, Lameire N, Aspin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney international supplements* 2012;2:1–138.
30. Mehta AB, Syeda SN, Wiener RS, et al. Epidemiological trends in invasive mechanical ventilation in the United States: a population-based study. *Journal of critical care* 2015;30:1217–1221. [PubMed: 26271686]
31. Kahn JM, Carson SS, Angus DC, et al. Development and validation of an algorithm for identifying prolonged mechanical ventilation in administrative data. *Health Services and Outcomes Research Methodology* 2009;9:117–132.
32. O'leary JG, Reddy KR, Garcia-Tsao G, et al. NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. *Hepatology* 2018;67:2367–2374. [PubMed: 29315693]

33. Sundaram V, Jalan R, Ahn J, et al. Class III (morbid) obesity is an independent risk factor for the development of acute on chronic liver failure in patients with decompensated cirrhosis. *Journal of Hepatology* 2018;68:S236.
34. Arroyo V, Moreau R, Jalan R, et al. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. *Journal of hepatology* 2015;62:S131–S143. [PubMed: 25920082]
35. Bernal W, Jalan R, Quaglia A, et al. Acute-on-chronic liver failure. *The Lancet* 2015;386:1576–1587.
36. Mathurin P, Mendenhall CL, Carithers RL Jr, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *Journal of hepatology* 2002;36:480–487. [PubMed: 11943418]
37. Mathurin P, O’grady J, Carithers RL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2010:
38. Kazis LE, Miller DR, Clark J, et al. Health-related quality of life in patients served by the Department of Veterans Affairs: results from the Veterans Health Study. *Archives of internal medicine* 1998;158:626–632. [PubMed: 9521227]
39. Fortney JC, Curran GM, Hunt JB, et al. Prevalence of probable mental disorders and help-seeking behaviors among veteran and non-veteran community college students. *General hospital psychiatry* 2016;38:99–104. [PubMed: 26598288]
40. Julapalli VR, Kramer JR, El-Serag HB. Evaluation for liver transplantation: adherence to AASLD referral guidelines in a large Veterans Affairs center. *Liver transplantation* 2005;11:1370–1378. [PubMed: 16184521]

Figure 1 –.

ACLF Events over Time per APASL (a) and EASL (b) Criteria - The probability of experiencing an ACLF event over time was significantly higher for patients with either alcoholic or hepatitis C plus alcoholic liver disease, as compared to other etiologies of liver disease. This was true in both APASL and EASL ACLF definitions.

Figure 2 –.

ACLF Survival over Time for APASL (a) and EASL (b) Events – The probability of ACLF survival was significantly lower through one year for patients with hepatitis C or non-alcoholic fatty liver disease, as compared to other etiologies of liver disease. This was true in both APASL and EASL ACLF definitions.

Figure 3 –.

Frequency of Organ Failures and Acute Decompensations in EASL ACLF. Kidney failure was the most common organ failure among all EASL ACLF grades (a), while infection was the most common acute decompensation in EASL grades 1 and 3 (b). Among patients EASL ACLF grade 3, kidney was the most common organ failure (c) and infection the most common acute decompensation (d) for all etiologies of liver disease.

Table 1 –

Patient Characteristics by ACLF Classification

Variable	EASL + APASL N = 783	EASL Alone N = 4,296	APASL Alone N = 574	No ACLF N = 74,730	p-value
Age, median (IQR)	58.0 (53.0, 61.0)	60.0 (56.0, 64.0)	58.0 (54.0, 62.0)	62.0 (57.0, 66.0)	<0.001
Age Category (years)					<0.001
<40	11 (1.4%)	12 (0.3%)	8 (1.4%)	639 (0.9%)	
40–65	712 (90.9%)	3,432 (79.9%)	520 (90.6%)	52,596 (70.4%)	
>65	60 (7.7%)	852 (19.8%)	46 (8.0%)	21,495 (28.8%)	
Male Sex	758 (96.8%)	4,217 (98.2%)	553 (98.1%)	72,421 (96.9%)	<0.001
Race					<0.001
White	392 (50.1%)	2,190 (51.0%)	291 (50.7%)	41,749 (55.9%)	
Black	140 (17.9%)	727 (16.9%)	90 (15.7%)	13,075 (17.5%)	
Hispanic	92 (11.7%)	512 (11.9%)	64 (11.1%)	6,851 (9.2%)	
Asian/PI	6 (0.8%)	58 (1.4%)	9 (1.6%)	1,031 (1.4%)	
Other/Unknown	153 (19.5%)	809 (18.8%)	120 (20.9%)	12,024 (16.1%)	
BMI Category					<0.001
Underweight (<18.5)	22 (2.8%)	123 (2.9%)	16 (2.8%)	2,130 (2.9%)	
Normal (18.5–24.9)	203 (26.2%)	1,031 (24.2%)	168 (29.4%)	19,224 (26.0%)	
Overweight (25–29.9)	275 (35.4%)	1,380 (32.4%)	218 (38.1%)	26,057 (35.2%)	
Obese (≥ 30)	276 (35.6%)	1,730 (40.6%)	170 (29.7%)	26,536 (35.9%)	
Liver Disease Etiology					<0.001
Hepatitis C	103 (13.2%)	648 (15.1%)	58 (10.1%)	13,150 (17.6%)	
Hepatitis B	16 (2.0%)	109 (2.5%)	20 (3.5%)	1,822 (2.4%)	
EtOH	309 (39.5%)	1,287 (30.0%)	202 (35.2%)	21,686 (29.0%)	
Hepatitis C + EtOH	244 (31.2%)	1,344 (31.3%)	203 (35.4%)	20,552 (27.5%)	
NAFLD	82 (10.5%)	778 (18.1%)	69 (12.0%)	14,964 (20.0%)	
Other	29 (3.7%)	130 (3.0%)	22 (3.8%)	2,556 (3.4%)	
Baseline MELD-Na	11.0 (9.0, 16.0)	9.0 (7.0, 13.0)	11.0 (8.0, 16.0)	8.0 (6.0, 11.0)	<0.001
Baseline CTP Class					<0.001
A	385 (49.2%)	2,983 (69.4%)	304 (53.0%)	61,496 (82.3%)	
B	365 (46.6%)	1,268 (29.5%)	248 (43.2%)	12,864 (17.2%)	
C	33 (4.2%)	45 (1.0%)	22 (3.8%)	370 (0.5%)	
Hypertension	667 (85.2%)	3,907 (90.9%)	485 (84.5%)	68,818 (92.1%)	<0.001
Diabetes Mellitus	387 (49.4%)	2,743 (63.9%)	247 (43.0%)	35,487 (47.5%)	<0.001
Chronic Kidney Disease	17 (2.2%)	258 (6.0%)	14 (2.4%)	5,509 (7.4%)	<0.001
Coronary Artery Disease	63 (8.0%)	840 (19.6%)	66 (11.5%)	14,965 (20.0%)	<0.001
Congestive Heart Failure	33 (4.2%)	549 (12.8%)	24 (4.2%)	7,642 (10.2%)	<0.001
Cerebrovascular Accident	9 (1.1%)	107 (2.5%)	4 (0.7%)	2,494 (3.3%)	<0.001
Atrial Fibrillation	28 (3.6%)	341 (7.9%)	10 (1.7%)	5,786 (7.7%)	<0.001
Pulmonary Embolism	2 (0.3%)	32 (0.7%)	6 (1.0%)	788 (1.1%)	0.037
On Anticoagulation	31 (4.0%)	516 (12.0%)	21 (3.7%)	2,884 (3.9%)	<0.001
Hepatocellular Carcinoma	59 (7.5%)	304 (7.1%)	62 (10.8%)	4,036 (5.4%)	<0.001

Variable	EASL + APASL N = 783	EASL Alone N = 4,296	APASL Alone N = 574	No ACLF N = 74,730	p-value
Liver Transplantation	32 (4.1%)	119 (2.8%)	24 (4.2%)	924 (1.2%)	<0.001

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2 –**ACLF Incidence and Mortality**

	Incidence		Mortality	
	Rate*	95% CI	28-day	90-day
APASL ACLF	5.7	5.4 – 6.0	41.9%	56.1%
EASL-CLIF ACLF (overall)	20.1	19.5 – 20.6	37.6%	50.4%
Infection	9.0	8.6 – 9.3	42.9%	52.7%
Ascites	5.9	5.6 – 6.2	37.9%	58.1%
GI bleed	3.5	3.3 – 3.8	36.9%	47.9%
Hepatic encephalopathy	6.9	6.5 – 7.2	33.1%	48.9%
Grade 1	9.3	9.0 – 9.7	19.3%	32.5%
Infection	4.1	3.8 – 4.3	18.5%	28.3%
Ascites	3.3	3.1 – 3.5	27.8%	47.5%
GI bleed	1.5	1.4 – 1.7	18.1%	30.5%
Hepatic encephalopathy	2.2	2.1 – 2.4	15.3%	30.2%
Grade 2	6.2	5.9 – 6.5	38.4%	53.3%
Infection	2.2	2.1 – 2.4	46.9%	59.1%
Ascites	1.7	1.5 – 1.8	43.2%	65.1%
GI bleed	1.1	1.0 – 1.3	34.7%	46.4%
Hepatic encephalopathy	3.1	2.9 – 3.3	28.5%	47.0%
Grade 3	4.5	4.3 – 4.8	74.3%	83.4%
Infection	2.6	2.4 – 2.8	77.1%	84.9%
Ascites	0.9	0.8 – 1.0	64.9%	84.2%
GI bleed	0.8	0.7 – 1.0	74.1%	81.6%
Hepatic encephalopathy	1.5	1.4 – 1.7	68.2%	80.0%
Any Inpatient Admission**			5.0%	12.1%
Infection			6.6%	15.6%
Ascites			10.0%	28.3%
GI bleed			4.5%	12.0%
Hepatic encephalopathy			8.2%	21.6%

* Rate presented as events per 1,000 persons per year

** Excluding admissions with EASL-CLIF ACLF

Table 3 –
ACLF Incidence and Mortality by Etiology of Liver Disease

	Etiology	Incidence		Mortality	
		Rate *	95% CI	28-day	90-day
APASL	Hepatitis C	4.1	3.5 – 4.7	53.4%	65.2%
	Hepatitis B	5.5	4.0 – 7.7	30.6%	47.2%
	EtOH	7.1	6.5 – 7.8	39.1%	50.5%
	Hepatitis C + EtOH	6.8	6.2 – 7.5	38.9%	54.4%
	NAFLD	3.4	2.9 – 4.0	51.0%	73.5%
	Other	5.0	3.8 – 6.6	39.2%	52.9%
	Overall	5.7	5.4 – 6.0	41.9%	56.1%
EASL-CLIF (all)	Hepatitis C	18.0	16.8 – 19.3	42.3%	57.8%
	Hepatitis B	18.0	15.1 – 21.5	36.0%	47.2%
	EtOH	20.8	19.8 – 21.8	35.3%	47.5%
	Hepatitis C + EtOH	22.4	21.3 – 23.5	33.9%	45.8%
	NAFLD	18.6	17.4 – 19.9	45.2%	59.2%
	Other	15.0	12.8 – 17.5	35.9%	45.9%
	Overall	20.1	19.5 – 20.6	37.6%	50.4%

* Rate presented as events per 1,000 persons per year

Table 4 –

Laboratory Profiles at the Time of ACLF Events

Lab Test, median (IQR)	EASL + APASL N = 783		EASL Alone N = 4,296	APASL Alone N = 574
	By EASL Timing	By APASL Timing		
AST	99.0 (61.0, 185.0)	98.0 (63.0, 174.0)	58.0 (36.0, 104.0)	84.0 (60.0, 143.0)
ALT	49.0 (31.0, 86.0)	49.0 (31.0, 82.0)	35.0 (22.0, 58.0)	45.0 (30.0, 67.0)
T Bili	12.1 (5.8, 17.2)	9.0 (5.6, 17.5)	2.0 (1.1, 4.0)	6.5 (4.9, 9.8)
Alkaline Phosphatase	121.0 (88.0, 183.0)	130.0 (95.0, 185.0)	110.0 (79.0, 161.0)	132.0 (97.0, 186.0)
Albumin	2.3 (1.9, 2.8)	2.3 (1.9, 2.7)	2.5 (2.1, 3.1)	2.3 (2.0, 2.7)
Creatinine	1.8 (1.1, 2.7)	1.2 (0.8, 2.3)	2.0 (1.6, 2.8)	0.8 (0.7, 1.1)
INR	2.3 (1.8, 2.8)	2.0 (1.7, 2.6)	1.5 (1.3, 2.2)	1.8 (1.6, 2.1)