Research Article
Cirrhosis

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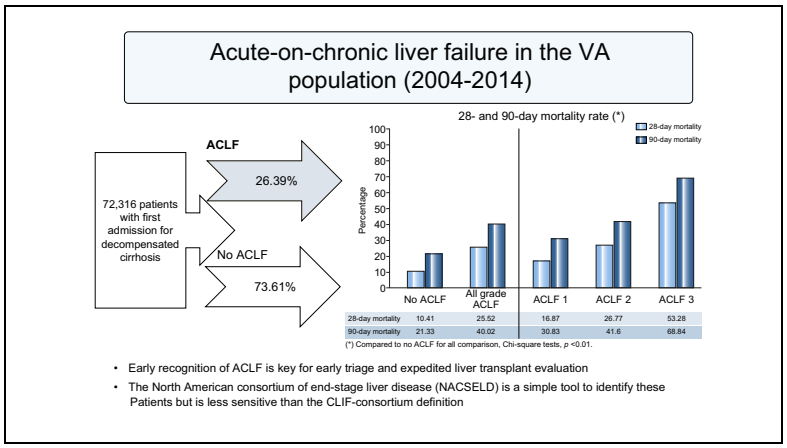
# Prevalence and short-term mortality of acute-on-chronic liver failure: A national cohort study from the USA

## Graphical abstract




## Highlights

- Of 72,316 ethnically diverse patients from 127 Veterans Affairs facilities in the US, 19,082 (26.39%) met ACLF criteria.
- Patients with ACLF had high 28- and 90-day mortality (25.52% and 40.02%, respectively).
- Mortality risk increased in parallel with the number of OFs, ranging from 17–53% at 28 days and 31–69% at 90 days.
- African-American race and being seen at a transplant centre were associated with a lower risk of ACLF mortality.

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## Lay summary

Acute-on-chronic liver failure (ACLF) is a condition marked by multiple organ failures in patients with cirrhosis and associated with a high risk of death. In this study of US patients hospitalised with cirrhosis, 1 in 4 patients developed ACLF. In total, 25% of patients with ACLF died within 1 month and 40% died within 3 months. Thus, early recognition of ACLF is important for the initiation of aggressive management, which is required to save these patients' lives.

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# Prevalence and short-term mortality of acute-on-chronic liver failure: A national cohort study from the USA

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**Background & Aims**: Acute-on-chronic liver failure (ACLF) is characterised by the presence of organ failure in patients with decompensated cirrhosis and is associated with high short-term mortality. However, there are limited data on the prevalence and short-term outcomes of ACLF in patients with cirrhosis seen in the US. We aimed to study the prevalence and risk factors associated with the development and short term mortality in a large cohort of patients in the US.

**Methods**: Using the US Department of Veterans Affairs (VA) Corporate Data Warehouse, we identified patients with ACLF during hospitalisation for decompensated cirrhosis at any of the 127 VA hospitals between January 1, 2004, and December 31, 2014. We examined the prevalence of ACLF and variables associated with 28- and 90-day mortality in ACLF, and trends in prevalence and survival over time.

**Results**: Of 72,316 patients hospitalised for decompensated cirrhosis, 19,082 (26.4%) patients met the criteria of ACLF on admission. Of these, 12.8% had 1, 10.1% had 2, and 3.5% had 3 or more organ failures. Overall, 25.5% and 40.0% of ACLF patients died within 28 days and 90 days of admission, respectively. Older age, White race, liver cancer, higher model for end-stage liver disease sodium corrected score, and non-liver transplant centre were associated with increased risk of death in ACLF. Over the study period, the prevalence of ACLF decreased, and all grades but ACLF-3 had improvement in survival.

**Conclusions**: In a US cohort of hospitalised patients with decompensated cirrhosis, ACLF was common and associated with high short-term mortality. Over a decade, ACLF prevalence decreased but survival improvement of ACLF-3 was not seen. Early recognition and aggressive management including timely referral to transplant centres may lead to improved outcomes in ACLF.

**Lay summary**: Acute-on-chronic liver failure (ACLF) is a condition marked by multiple organ failures in patients with cirrhosis and associated with a high risk of death. In this study of US patients hospitalised with cirrhosis, 1 in 4 patients developed ACLF. In total, 25% of patients with ACLF died within 1 month and 40% died within 3 months. Thus, early recognition of ACLF is important for the initiation of aggressive management, which is required to save these patients' lives.



## Introduction

Acute-on-chronic liver failure (ACLF) is a recently recognised condition characterised by multiorgan failure in patients with decompensated cirrhosis and associated with high short-term mortality.[1–3]

Previous research has provided insight into the prevalence and outcomes of patients with ACLF, but most studies were conducted in European cohorts of patients with cirrhosis;[2] data from the United States are mainly limited to a single cohort of fewer than 3,000 patients with cirrhosis.[4] In addition, these studies have been conducted in highly specialised centres, with possibly limited generalisability to patients seen outside the tertiary care settings. Hence, only limited data are available on the prevalence and short-term outcomes of ACLF in patients with cirrhosis seen in the United States.

Studies show that the number of organ failures – used to define the stage of disease – is the strongest predictor of short-term mortality in ACLF. Other factors, including patient demographics, aetiology of cirrhosis, and type of precipitating factors have been variably implicated in impacting outcomes in ACLF. Healthcare system factors also predict the quality and outcomes of patients with cirrhosis in general. Yet, there is little

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information about which of these factors may influence ACLF outcomes and even less information about how the effect of these factors varies by ACLF stage overall and over time.

We aimed to determine the prevalence and short-term mortality of ACLF in a large cohort of patients hospitalised with decompensated cirrhosis in any of the 127 Veterans Affairs (VA) hospitals between 2004 and 2014. We also examined the role of patient and healthcare system factors in predicting short-term mortality in ACLF. Last, because recent data show decreasing inpatient mortality in patients hospitalised with cirrhosis over time, we examined time trends in mortality of patients with ACLF.

## Patients and methods

### Data source

We extracted data from the VA Corporate Data Warehouse (CDW) to derive the cohort and study variables. The CDW includes separate files extracted from the VA electronic medical record in a relational database containing patient demographics and outpatient and inpatient utilisation including diagnosis (International Classification of Diagnosis, ninth revision [ICD-9]) and Current Procedural Terminology (CPT) codes, laboratory data, and vital status information. Vital status combines information from Medicare, VA, Social Security, and VA compensation and pension benefits to determine date of death (sensitivity 98.3%; specificity 99.8% relative to National Death Index). We used the CDW inpatient and VA purchased care files to derive index hospitalisation with cirrhosis and the vital status file to determine date of death used to calculate mortality rates. VA purchased care files include services paid by but rendered outside the VA, including acute hospitalisations.

For further details regarding the materials used, please refer to the CTAT table and supplementary information.

### Study population

We identified patients who had their first admission with decompensated cirrhosis at any of the 127 VA hospitals between January 1, 2004 and December 31, 2014. Patients had to be hospitalised for at least 24 hours to be included in the analyses; this criterion is consistent with the inclusion criteria of the CANONIC study, which described the natural history of 1,343 hospitalised patients with cirrhosis and was conducted by the European Association for the Study of the Liver-Chronic Liver Failure.[2] For patients with multiple hospitalisations, we selected the first within the study time frame for this study. We excluded patients who had received liver transplantation prior to their index hospitalisation.

We used 2 criteria to define decompensated cirrhosis, as previously described.[2] Specifically, we classified patients as having decompensated cirrhosis if they had at least one ICD-9 code for any of the following cirrhosis complications: ascites, hepatic encephalopathy, hepatocellular carcinoma (HCC), varices or variceal bleeding, portal hypertension, hepatorenal syndrome, or hepatopulmonary syndrome; or, if they had at least one ICD-9 code for cirrhosis with either ICD-9 code/s for infection or gastrointestinal bleeding during the index hospitalisation (Table S1). It is plausible that HCC was not an original component of the CANONIC study and that use of HCC as one of the inclusion criteria might capture some patients without underlying cirrhosis. We opted to include patients with HCC in the primary analysis because cirrhosis is the strongest risk factor for the development of HCC. However, we removed patients who met the cohort inclusion criteria on the basis of HCC diagnosis alone (without any other cirrhosis complications) as part of a sensitivity analysis.

We adapted the definitions used in the CANONIC study to derive organ failure in our cohort based on blood pressure or laboratory values within 24 hours of admission or ICD/CPT codes during their first hospital admission (Table S2). We defined liver failure as serum bilirubin value ≥12 mg/dl; kidney failure as serum creatinine ≥2.0 mg/dl or use of renal replacement therapy or, as surrogate, end-stage renal disease (based on ICD-9 or CPT codes); cerebral failure as presence of hepatic encephalopathy as diagnosis code during hospital stay;[5] coagulation failure as serum international normalised ratio (INR) ≥2.5; circulation failure as mean arterial pressure of <60 mmHg and/or use of any doses of intravenous epinephrine, norepinephrine, dobutamine, dopamine, vasopressin; and respiratory failure as need for mechanical ventilation (based on ICD-9 or CPT codes).

We defined ACLF as presence of one or more organ failures defined after 24 hours of admission. Patients were further categorised as ACLF grades 1, 2, or 3, if they have 1, 2, or ≥3 organ failures, respectively. For ACLF-1, we adapted the CANONIC study definition as reported by Moreau *et al.*[2] (i) patients with single kidney failure, (ii) patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dl, and (iii) patients with single cerebral failure who had a serum creatinine level ranging from 1.5 to 1.9 mg/dl.

In addition, to compare our data with the North American Consortium for the Study of End-Stage Liver Disease (NACSELD), limited to 2,675 patients seen in tertiary care referral centres, we also provided an estimate of the prevalence, 28- and 90-day transplant-free mortality using the NACSELD-ACLF definition, requiring 2 of 4 organ failures as we have previously defined in our paper (kidney, brain, circulatory, and respiratory failures; Table S2).[4] Unless specified otherwise, ACLF will be defined by the CANONIC study criteria; by contrast, when stated NACSELD-ACLF criteria will be used to represent the NACSELD definition.

### Primary outcome, patient, and hospital characteristics

The primary outcome was transplant-free mortality within the 28 and 90 days after the date of first admission for decompensated cirrhosis.

We obtained age, sex, race, blood pressure, and laboratory values from CDW. We defined hepatitis C virus (HCV) based on a positive HCV ribonucleic acid test, and alcohol-related liver disease based on at least one instance of an ICD-9 code for alcohol use disorders or an Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) ≥4 or AUDIT ≥8, at any point prior to the first admission for decompensated cirrhosis. We defined the following injury/trigger factors: infection, gastrointestinal bleeding, and active alcohol use. Active alcohol use was further defined when the patient had any alcohol code and/or AUDIT-C ≥4 or AUDIT ≥8 within 1 year prior to the first admission.

We calculated the model for end-stage liver disease sodium corrected (MELD-Na) using laboratory values for bilirubin, creatinine, INR, and serum sodium on the first value within 24 hours. If several values were present within 24 hours, we took the maximum bilirubin, creatinine, and INR, and lowest sodium values. We also examined 2 facility-level factors: whether the facility was 1 of the 6 liver transplant centres in the country for Veterans, and facility complexity (high, medium, and low)

**Table 1. Baseline characteristics of Veterans admitted with decompensated cirrhosis from 2004 to 2014 (absence *vs.* presence of ACLF).**

| | No ACLF | ACLF all grades | *p* value* |
|---|---|---|---|
| Sample, N (%) | 53,234 (73.61%) | 19,082 (26.39) | |
| Age (years), median (p25–p75) | 60.92 (55.73–66.95) | 62.31 (56.86–96.78) | <0.0001 |
| Male sex, n (%) | 51,920 (97.5) | 18,713 (98.1) | <0.0001 |
| Race/ethnicity, n (%) | | | <0.0001 |
| African American | 9,138 (17.17) | 4,628 (24.25) | |
| White | 38,754 (72.80) | 12,504 (65.53) | |
| Other | 1,463 (2.75) | 504 (2.64) | |
| Missing | 3,879 (7.29) | 1,446 (7.58) | |
| Body mass index, n (%) | | | <0.0001 |
| <18.5 kg/m$^2$ | 207 (0.39) | 74 (0.39) | |
| ≥18.5 and <25 kg/m$^2$ | 7,099 (13.34) | 2,033 (10.65) | |
| ≥25 and <30 kg/m$^2$ | 13,868 (26.05) | 4,735 (24.81) | |
| ≥30 kg/m$^2$ | 21,322 (40.05) | 8,919 (46.74) | |
| Missing | 10,738 (20.17) | 3,321 (17.40) | |
| Cirrhosis aetiology | | | <0.0001 |
| None | 17,928 (33.68) | 8,379 (43.91) | |
| Alcohol | 16,376 (30.76) | 5,379 (28.19) | |
| HCV | 7,704 (14.47) | 2,450 (12.84) | |
| Both | 11,226 (21.09) | 2,874 (15.06) | |
| Cirrhosis complications, n (%) | | | |
| Ascites | 26,809 (50.36) | 11,478 (60.15) | <0.0001 |
| Hepatic encephalopathy | 10,481 (19.69) | 6,870 (36.00) | <0.0001 |
| Hepatocellular carcinoma | 8,819 (16.57) | 1,641 (8.60) | <0.0001 |
| Varices | 11,199 (21.04) | 3,310 (17.35) | <0.0001 |
| Potential precipitating events of ACLF | | | |
| Bacterial infection | 5,587 (10.50) | 2,762 (14.47) | <0.0001 |
| Gastrointestinal haemorrhage | 4,596 (8.63) | 1,632 (8.55) | 0.732 |
| Alcoholism 1 year prior to cirrhosis index date | 19,338 (36.33) | 5,469 (28.66) | <0.0001 |
| Infection or gastrointestinal bleeding or alcohol | 25,192 (47.32) | 7,936 (41.59) | <0.0001 |
| Organ failures | | | |
| Liver | 1,144 (2.15) | 2,342 (12.27) | <0.0001 |
| Kidney | 0 (0.00) | 13,718 (71.89) | <0.0001 |
| Cerebral | 10,481 (19.69) | 6,870 (36.00) | <0.0001 |
| Coagulation | 1,314 (2.47) | 2,644 (13.86) | <0.0001 |
| Circulation | 602 (1.13) | 3,362 (17.62) | <0.0001 |
| Lungs | 918 (1.72) | 3,227 (16.91) | <0.0001 |
| Arterial pressure (mmHg), median (p25–p75) | 93.17 (84.33–102.33) | 87.17 (76.83–98.50) | <0.0001 |
| Laboratory data on admission, median (p25–p75) | | | |
| Serum bilirubin (mg/dl) | 1.30 (0.80–2.60) | 1.50 (0.80–4.10) | <0.0001 |
| INR | 1.24 (1.10–1.46) | 1.40 (1.20–1.80) | <0.0001 |
| Serum creatinine (mg/dl) | 0.90 (0.76–1.14) | 2.01 (1.30–3.06) | <0.0001 |
| MELD-Na score | 15.37 (12.20–19.58) | 25.62 (22.21–30.06) | <0.0001 |
| Healthcare system factors, n (%) | | | |
| Facility complexity model score | | | <0.0001 |
| Low complexity | 1,935 (3.63) | 505 (2.65) | |
| Median complexity | 4,322 (8.12) | 1,457 (7.64) | |
| High complexity | 46,977 (88.25) | 17,120 (89.72) | |
| Live transplant centre | 5,140 (9.66) | 1,791 (9.39) | 0.278 |
| Time trend (year diagnosis) n (%) | | | <0.0001 |
| 2004–06 | 14,149 (26.58) | 5,424 (28.24) | |
| 2007–08 | 9,291 (17.45) | 3,537 (18.54) | |
| 2009–10 | 10,292 (19.33) | 3,650 (19.13) | |
| 2011–12 | 10,764 (20.22) | 3,753 (19.67) | |
| 2013–14 | 8,738 (16.41) | 2,718 (14.24) | |

ACLF, acute-on-chronic liver failure; HCV, hepatitis C virus; INR, international normalised ratio; MELD-Na, model for end-stage liver disease sodium corrected.
*Laboratory variables were compared medians by using non-parametric tests.

based on the VA policy and the presence of complexity of patients, services, and levels of intensive care units,[6] and whether the facility was 1 of the 6 liver transplant centres in the country for Veterans (Table S3).

### Statistical analyses

We compared patients with and without ACLF with respect to demographic and clinical characteristics as well as transplant-free 28- and 90-day mortality. We also compared these characteristics among patients with 3 grades of ACLF. We used Chi-square test for categorical variables and parametric and non-parametric tests for continuous variables depending whether the variables were normally distributed or not. We constructed logistic regression models to evaluate the possible predictors/associations with mortality ACLF. We used a stepwise approach and included only clinically meaningful variables in the final model to understand what factors were independently associated with 28- and 90-day mortality. We

**Table 2. Baseline characteristics of Veterans admitted with decompensated cirrhosis from 2004 to 2014 (grades of ACLF).**

| | ACLF grade 1 | ACLF grade 2 | ACLF grade 3 | *p* value* |
|---|---|---|---|---|
| Sample, N (%) | 9,239 (12.78) | 7,298 (10.09) | 2,545 (3.52) | |
| Age (years), median (p25–p75) | 63.59 (58.01–72.79) | 61.22 (56.02–67.21) | 61.14 (55.78–67.03) | 0.019 |
| Male sex, n (%) | 9,085 (98.34) | 7,145 (97.93) | 2,483 (97.56) | <0.0001 |
| Race/ethnicity, n (%) | | | | <0.0001 |
| African American | 2,619 (28.35) | 1,460 (20.01) | 549 (21.57) | |
| White | 5,761 (62.36) | 5,048 (69.17) | 1,695 (66.60) | |
| Other | 246 (2.66) | 197 (2.70) | 61 (2.40) | |
| Missing | 613 (6.63) | 593 (8.13) | 240 (9.43) | |
| Body mass index, n (%) | | | | <0.0001 |
| <18.5 kg/m$^2$ | 32 (0.35) | 28 (0.38) | 14 (0.55) | |
| ≥18.5 and <25 kg/m$^2$ | 954 (10.33) | 783 (10.73) | 296 (11.63) | |
| ≥25 and <30 kg/m$^2$ | 2,351 (25.45) | 1,738 (23.81) | 656 (25.78) | |
| ≥30 kg/m$^2$ | 4,554 (49.29) | 3,310 (45.35) | 1,055 (41.45) | |
| Missing | 1,348 (14.59) | 1,439 (19.72) | 534 (20.98) | |
| Cirrhosis aetiology | | | | <0.0001 |
| None | 4,510 (48.81) | 2,823 (38.68) | 1,046 (41.10) | |
| Alcohol | 2,111 (22.85) | 2,330 (31.93) | 938 (36.86) | |
| HCV | 1,256 (13.59) | 979 (13.41) | 215 (8.45) | |
| Both | 1,362 (14.74) | 1,166 (15.98) | 346 (13.60) | |
| Cirrhosis complications, n (%) | | | | <0.0001 |
| Ascites | 5,509 (59.63) | 4,599 (63.02) | 1,370 (53.83) | |
| Hepatic encephalopathy | 1,098 (11.88) | 4,307 (59.02) | 1,465 (57.56) | |
| Hepatocellular carcinoma | 880 (9.52) | 626 (8.58) | 135 (5.30) | |
| Varices | 1,253 (13.56) | 1,689 (23.14) | 368 (14.46) | |
| Potential precipitating events of ACLF | | | | <0.0001 |
| Bacterial infection | 971 (10.51) | 1,196 (16.39) | 595 (23.38) | |
| Gastrointestinal haemorrhage | 551 (5.96) | 750 (10.28) | 331 (13.01) | |
| Alcoholism 1 year prior to cirrhosis index date | 2,120 (22.95) | 2,426 (33.24) | 923 (36.27) | |
| Infection or gastrointestinal bleeding or alcohol | 3,091 (33.46) | 3,473 (47.59) | 1,372 (53.91) | |
| Organ failures | | | | <0.0001 |
| Liver | 156 (1.69) | 1,284 (17.59) | 902 (35.44) | |
| Kidney | 7,293 (78.94) | 4,500 (61.66) | 1,925 (75.64) | |
| Cerebral | 1,098 (11.88) | 4,307 (59.02) | 1,465 (57.56) | |
| Coagulation | 370 (4.00) | 1,342 (18.39) | 932 (36.62) | |
| Circulation | 176 (1.90) | 1,579 (21.64) | 1,607 (63.14) | |
| Lungs | 146 (1.58) | 1,584 (21.70) | 1,497 (58.82) | |
| Arterial pressure (mmHg), median (p25–p75) | 89.17 (78.67–101.00) | 87.00 (77.00–97.33) | 81.00 (70.67–92.00) | <0.0001 |
| Laboratory data on admission, median (p25–p75) | | | | |
| Serum bilirubin (mg/dl) | 1.10 (0.60–2.10) | 2.10 (1.00–6.40) | 4.70 (1.40–16.30) | <0.0001 |
| INR | 1.29 (1.10–1.50) | 1.50 (1.24–2.02) | 1.90 (1.40–2.81) | <0.0001 |
| Serum creatinine (mg/dl) | 2.21 (1.70–3.50) | 1.50 (0.90–2.50) | 2.20 (1.20–3.30) | <0.0001 |
| MELD-Na score | 23.99 (21.35–27.25) | 26.93 (22.71–31.10) | 32.24 (26.33–37.40) | <0.0001 |
| Healthcare system factors, n (%) | | | | |
| Facility complexity model score | | | | 0.090 |
| Low complexity | 248 (2.68) | 203 (2.78) | 54 (2.12) | |
| Median complexity | 737 (7.98) | 548 (7.51) | 172 (6.76) | |
| High complexity | 8,254 (89.34) | 6,547 (89.71) | 2,319 (91.12) | |
| Liver transplant centre | 848 (9.18) | 685 (9.39) | 258 (10.14) | 0.340 |
| Time trend (year diagnosis), n (%) | | | | <0.0001 |
| 2004–06 | 2,501 (27.07) | 2,183 (29.91) | 740 (29.08) | |
| 2007–08 | 1,687 (18.26) | 1,360 (18.64) | 490 (19.25) | |
| 2009–10 | 1,733 (18.76) | 1,419 (19.44) | 498 (19.57) | |
| 2011–12 | 1,894 (20.50) | 1,396 (19.13) | 463 (18.19) | |
| 2013–14 | 1,424 (15.41) | 940 (12.88) | 354 (13.91) | |

ACLF, acute-on-chronic liver failure; HCV, hepatitis C virus; INR, international normalised ratio; MELD-Na, model for end-stage liver disease sodium corrected.
*Laboratory variables were compared medians by using non-parametric tests.

also examined temporal trends in the yearly prevalence and mortality of ACLF across the 10-year period. We first fitted a logistical regression model with mortality rate at 28 and 90 days as the binary outcome, and time (year) as a predictor, and subsequently fitted a hierarchical generalised linear model to account for the variance in patient outcomes within time and between patients. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The current analytical approach was approved by the Baylor-VA Medical Center institutional review board.

## Results

### Prevalence of ACLF and organ failure in the VA population

We identified 72,316 patients who were admitted for >24 hours with an episode of decompensated cirrhosis between 2004 and

2014. Of these, 19,082 patients (26.4%) met the criteria for ACLF: grade 1 ACLF in 9,239 (12.8%), grade 2 in 7,298 (10.1%), and grade 3 in 2,545 (3.5%) patients (Tables 1 and 2). Given the Veteran population, 98.08% of patients with ACLF were male; approximately one-quarter of patients with ACLF (24.3%) were African Americans (AAs), 46.7% had a body mass index ≥30 kg/m$^2$, 60.2% had ascites, 36.0% hepatic encephalopathy, 17.4% varices and/or variceal bleeding, and 12.5% spontaneous bacterial peritonitis. Compared with 53,234 patients with no ACLF, patients with ACLF were more likely to be older, AA, and to have ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome. Most patients in both groups had alcohol or HCV as the main underlying cause of cirrhosis; however, the presence of either alcohol or HCV was more common in patients without ACLF than in those with ACLF. Gastrointestinal bleeding, infection, and alcohol abuse were the precipitating events in 41.6% of patients with ACLF, with excessive alcohol use in the last year being the most common trigger (28.7%). In patients with ACLF, kidney failure (71.9%) and cerebral failure (36.0%) were the most common organ failures. As expected, patients with ACLF had higher levels of serum bilirubin, creatinine, and end-stage liver disease (MELD-Na) score than patients without. Similar results were also observed by ACLF grades in terms of proportion of AAs, prevalence of hepatic decompensation, and causes of cirrhosis; however, compared with ACLF-1, patients with ACLF-2 and ACLF-3 had more prevalence of bacterial infection (10.5% for ACLF-1 compared with 16.4% and 23.38% for ACLF-2 and ACLF-3, respectively), alcoholism 1 year prior to admission (22.9% for ACLF-1, compared to 33.2% and 36.8 for ACLF-2 and ACLF-3, respectively).

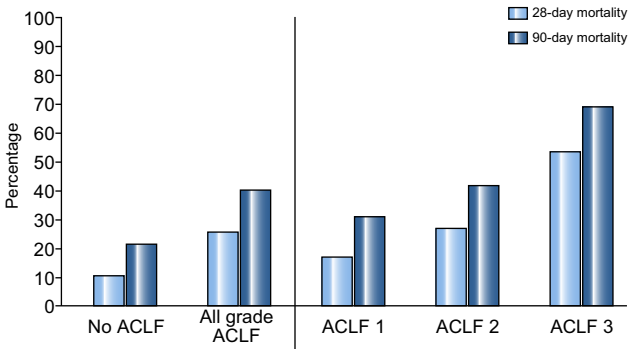
### Mortality of ACLF

In total, 10,411 patients died within 28 days and 19,267 within 90 days. The 28-day mortality was higher in patients with ACLF than in those without (25.5% *vs.* 10.4%, $p$ <0.01). The risk of 28-day transplant-free mortality increased with severity of ACLF; this risk was 16.87% in patients with ACLF-1, 26.8% in patients with ACLF-2, and 53.3% in patients with ACLF-3, respectively. At 90 days, 40.0% in the ACLF group died compared with 21.3% of participants without ACLF. A similar trend was seen with increasing grade of organ failures: for 30.8%, 41.6%, and 68.8% patients were dead 90 days in ACLF-1, ACLF-2, and ACLF-3, respectively (Fig. 1).

Removing 1,429 patients who met the cohort inclusion criterion on the basis of HCC alone (without any other cirrhosis complications) did not change the study results (Tables S4–5 and Fig. S1).

### Other patient and facility factors associated with ACLF mortality

In patients with ACLF, the presence of 2 or 3+ organ failures had a 1.89 (95% CI 1.74–2.05) and 4.50 (95% CI 4.04–5.01) higher odds of 28-day mortality compared with ACLF-1. Increasing age (adjusted odds ratio [OR] 1.03, 95% CI 1.02–1.03), presence of HCC (adjusted OR 1.70, 95% CI 1.50–1.92), and higher MELD-Na score (adjusted OR 1.05 per unit increase, 95% CI 1.04–1.06) were associated with higher odds of mortality. By contrast, AAs (*vs.* Whites), HCV as the underlying diagnosis, or presence of varices was associated with lower likelihood of mortality in ACLF. Hospital complexity was not an independent predictor of death in patients with ACLF (Table 3). Patients hospitalised in transplant centres had 20% lower odds of dying within




| | No ACLF | All grade ACLF | ACLF 1 | ACLF 2 | ACLF 3 |
|---|---|---|---|---|---|
| 28-day mortality | 10.41 | 25.52 | 16.87 | 26.77 | 53.28 |
| 90-day mortality | 21.33 | 40.02 | 30.83 | 41.6 | 68.84 |

**Fig. 1. Mortality rate* at 28 and 90 days in patients with and without ACLF and by grade.** To examine the difference between ACLF and ACLF grades, the independent Chi-square analysis was used. ACLF, acute-on-chronic liver failure. (*) Compared to no ACLF for all comparison, Chi-square tests, $p$ <0.01.

28 days than patients in non-transplant facilities (OR 0.80, 95% CI 0.63–1.01) and 19% lower odds of dying at 90 days (OR 0.81, 95% CI 0.67–0.98; Fig. 2). Similar findings were observed for 90-day mortality (Table 3).

We examined the race effect in an exploratory analysis. We compared clinical characteristics of AA *vs.* Whites overall and in groups defined based on ACLF. Overall, we found that prevalence of ACLF was higher in AA compared with Whites (33.62 *vs.* 24.39%, respectively, $p$ <0.0001). As reported in Tables S6 and S7, AA with ACLF were younger; had a higher prevalence of HCV, alcohol, or both; and a higher prevalence of HCC but lower prevalence of ascites, hepatic encephalopathy, and varices than Whites with ACLF. AAs were also more likely to have kidney failure, higher MELD-Na scores, and more likely to be admitted to a higher facility complexity/transplant centre than Whites. In terms of ACLF grade, AAs were more likely to have ACLF-1 than Whites (19.03% *vs.* 11.24%, respectively). Within each ACLF grade, and after adjusting by clinically relevant confounders, AA had a lower mortality risk at 28 and 90 days for ACLF-1 and at 28 days for ACLF-2 compared with Whites.

### Comparison between ACLF-CANONIC and ACLF-NACSELD

Of the 19,082 patients who met the CANONIC study criteria for ACLF, 7,127 (37.4%) met NACSELD criteria, whereas 11,955 (62.6%) did not meet NACSELD criteria. Given that NACSELD criteria are more restrictive, all patients meeting NACSELD criteria were captured by the CANONIC study criteria (Tables S8–9 and Fig. 3). Among patients meeting NACSELD criteria, 5,685 had 2 organ failures (7.9%), 1,254 3 (1.7%), and 188 had 4 organ failures (0.3%). The ACLF-NACSELD 28-day mortality was higher compared with the CANONIC study criteria in both patients without ACLF (12.4% *vs.* 10.4%) and those with ACLF (32.9% *vs.* 25.5%) (Fig. S2). Compared with patients meeting NACSELD criteria, those who did not meet the criteria were less likely to have infection, gastrointestinal bleeding, cerebral failure, and had lower MELD-Na; however, they were more likely to be AA, have alcohol abuse over the last year, and have liver and coagulation failure (Table S8). Of the 11,955 patients who did not meet NACSELD criteria, 77% had ACLF-1, 21% ACLF-2, and 2% ACLF-3. The 28- and 90-day mortality for this group (*i.e.* identified by the CANONIC study but not according to NACSELD criteria) was 21.07% and 35.27%, respectively, and significantly

**Table 3. Predictors of mortality among patients with ACLF.**

| | 28-day mortality OR (95% CI) | 90-day mortalityOR (95% CI) |
|---|---|---|
| ACLF grades (reference ACLF-1) | | |
| ACLF grade 2 | 1.89 (1.74–2.05) | 1.77 (1.65–1.90) |
| ACLF grade 3 | 4.50 (4.04–5.01) | 4.34 (3.89–4.83) |
| Demographics | | |
| Age (years) | 1.03 (1.02–1.03) | 1.03 (1.03–1.04) |
| Male *vs.* female | 1.14 (0.87–1.49) | 1.14 (0.90–1.45) |
| Race/Ethnicity (reference = White) | | |
| African American | 0.88 (0.81–0.97) | 0.88 (0.81–0.95) |
| Other | 0.93 (0.74–1.17) | 0.95 (0.77–1.15) |
| Unknown | 1.97 (1.74–2.24) | 2.34 (2.07–2.65) |
| Aetiology (reference = HCV) | | |
| None | 1.40 (1.23–1.59) | 1.36 (1.22–1.52) |
| Alcohol | 1.43 (1.23–1.66) | 1.40 (1.23–1.59) |
| Alcohol and HCV | 1.13 (0.96–1.32) | 1.07 (0.93–1.23) |
| Complications from cirrhosis | | |
| Ascites | 0.77 (0.72–0.83) | 0.99 (0.93–1.06) |
| Hepatocellular carcinoma | 1.70 (1.50–1.92) | 1.67 (1.49–1.87) |
| Varices | 0.31 (0.28–0.35) | 0.32 (0.29–0.35) |
| Triggers (reference = none) | | |
| Gastrointestinal bleeding | 1.05 (0.91–1.19) | 1.07 (0.94–1.21) |
| Infection | 1.25 (1.01–1.53) | 1.36 (1.14–1.63) |
| Alcohol use (within the year prior to admission) | 0.99 (0.87–1.11) | 1.00 (0.89–1.11) |
| Gastrointestinal bleeding or infection or alcohol use | 1.40 (1.22–1.62) | 1.37 (1.20–1.56) |
| MELD-Na score | 1.05 (1.04–1.06) | 1.05 (1.04–1.05) |
| Facility complexity score (reference = high) | | |
| Low | 0.98 (0.76–1.26) | 0.93 (0.75–1.17) |
| Median | 0.98 (0.82–1.16) | 0.98 (0.84–1.13) |
| Liver transplant facility (reference = no liver transplant) | 0.80 (0.63–1.01) | 0.81 (0.67–0.99) |

Results of multivariate logistic regression model that adjusted for all variables in the table.
ACLF, acute-on-chronic liver failure; HCV, hepatitis C virus; MELD-Na, model for end-stage liver disease sodium corrected; OR, odds ratio.

higher than corresponding estimates for patients without ACLF (10.41% and 21.57%, respectively; Table S9).

### Trends in ACLF prevalence and mortality between 2004 and 2014

The overall prevalence of ACLF gradually decreased from 27.0% (95% CI 26.0–28.1%) in 2004 to 22.17% (95% CI 20.9–23.5%) in 2014. The prevalence of ACLF-1 and ACLF-3 remained stable, whereas that of ACLF-2 decreased from 11.1% in 2004 to 7.4% in 2014. In patients without ACLF, 28-day mortality fell from 11.2% in 2004 to 8.1% in 2014. We found a similar decline in 28-day mortality in patients with ACLF-1 and ACLF-2: from 18.9% to 11.1% in ACLF-1 from 2004 to 2014, and from 28.7% to 24.4% in ACLF-2 from 2004 to 2014. However, there was no significant temporal change in the 28- or 90-day transplant-free mortality in patients with ACLF-3 (Fig. 4 and Table S10).

## Discussion

We report 3 major findings in 72,316 patients with first episode of decompensated cirrhosis over 10 years. First, ACLF was present in 26.39% (n = 19,082) of patients admitted with decompensated cirrhosis between 2004 and 2014 in VA hospitals. The most common underlying predisposing liver disease in ACLF was alcohol or hepatitis C (41.0%), whereas infection, gastrointestinal bleeding, or active alcohol use was identified in 41.6% as probable precipitating factors. Second, one-quarter of these patients (25.5%, n = 4,869) died within 28 days of admission and almost one-half in 90 days (40.0%, n = 7,636). The presence of 3 or more organ failures was associated with the highest 28- and 90-day mortality risk (53.3% and 68.8%, respectively). However, we also found several patient- and institution-level factors that were associated with suboptimal outcomes in patients with ACLF. Specifically, in addition to older age, White race/ethnicity, presence of HCC and MELD-Na, and being at a non-transplant facility were associated with higher mortality risk at 90 days but not at 28 days. Third, over a period of 10 years, ACLF prevalence decreased but mortality for ACLF-3 increased despite improvements in medical care and access to transplantation.

Overall, ACLF was more common in our population (26.39% *vs.* 22.56%) than data reported in the CANONIC study. However, most of this difference was due to the higher prevalence of ACLF-1 (15.8 *vs.* 12.78 in the CANONIC study). Furthermore, among patients with ACLF, mortality was lower in our cohort than in the CANONIC cohort (28-day mortality 25.52% *vs.* 32.8%; and 90-day mortality 40.02% *vs.* 51.2%). Differences in demographic factors (age and race), underlying cause of cirrhosis, triggers, and organ failure distribution likely explain the observed differences in the prevalence and outcomes of ACLF in the 2 studies. For example, compared with the CANONIC study, our patients with ACLF were older (62.3 *vs.* 64.4 years), more likely to be AAs (0% *vs.* 17%), and less likely to have alcohol as the cause of cirrhosis (28.19% *vs.* 60.3% with or without HCV). Furthermore, the precipitating trigger was less likely to be infectious (14.47% *vs.* 32.6%) or gastrointestinal bleeding (8.55% *vs.* 13.2%), but more likely to be recent alcohol abuse (28.66% *vs.* 24.5% at 3 months) in our study. With regard to organ failures, our cohort was more likely to have kidney (71.89% *vs.* 55.8%), cerebral (36.00% *vs.* 24.1%), coagulation (13.86% *vs.* 27.7%), and lung (16.91% *vs.* 9.2%) failures, but was less likely to have liver (12.27% *vs.* 43.6%) and circulatory failures (17.62% *vs.* 16.8%).

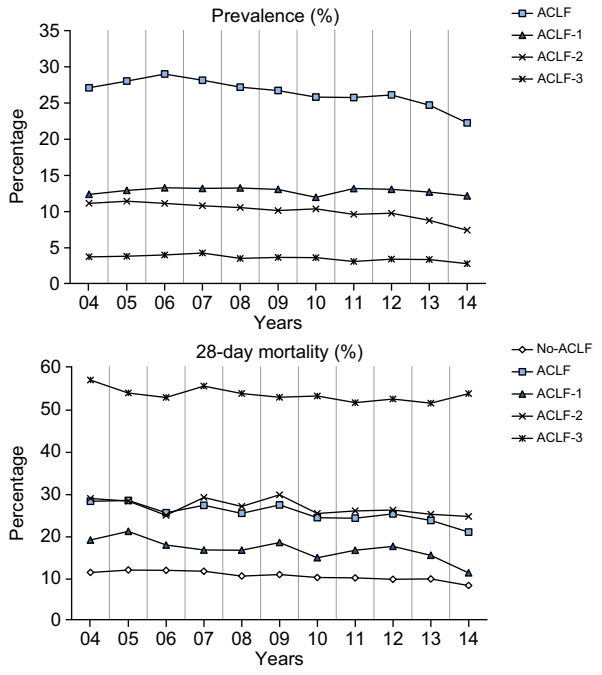
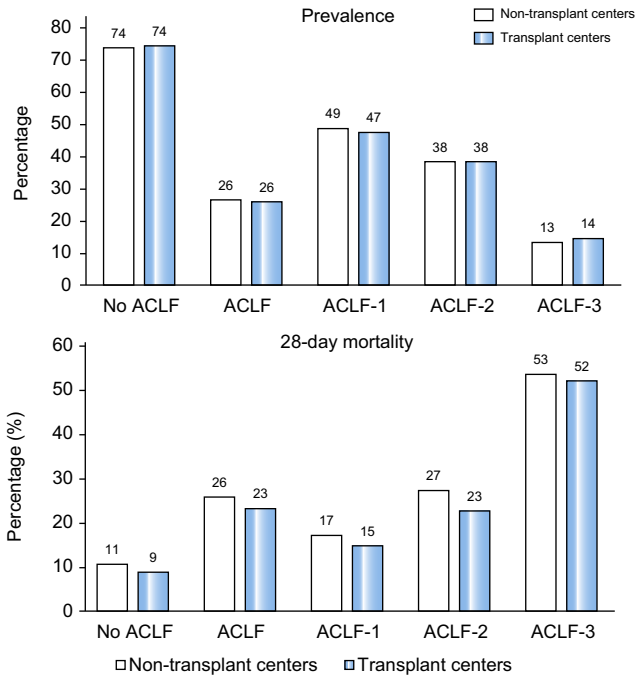



**Fig. 2. Prevalence of ACLF and 28-day mortality in patients with ACLF hospitalised at VA non-transplant *vs.* transplant centres.** To examine the difference between ACLF and ACLF grades, the independent Chi-square analysis was used for the categorical variables. ACLF, acute-on-chronic liver failure. Linear trends were significant at $p$ <0.05, except for ACLF-3 mortality.




| Prevalence non-transplant *vs.* transplant centers | $p$-values |
|---|---|
| ACLF (yes/no) | 0.278 |
| ACLF grade | 0.348 |
| 28-day mortality non-transplant *vs.* transplant centers | |
| ACLF (yes/no) | 0.501 |
| ACLF grade | 0.161 |

**Fig. 3. Comparison of patients with ACLF defined based on the CANONIC *vs.* NACSELD study criteria.** ACLF, acute-on-chronic liver failure; CANONIC, Acute-on-Chronic Liver Failure in Cirrhosis; NACSELD, North American Consortium for the Study of End-Stage Liver Disease.

Some of the differences may also be related to different coding schemes, inclusion of patients admitted at both tertiary and non-tertiary hospitals, and relatively early stages of decompensated cirrhosis (all patients had first decompensation) in our cohort. Despite these differences, both studies underscore the prognostic significance of organ failure in cirrhosis by demonstrating a progressive increase in mortality risk with additional organ failures.

The operational definitions of ACLF in the CANONIC and NACSELD studies differ. Whereas the CANONIC study criteria include up to 6 organ failures using a modification of the well-established sequential organ failure assessment,[7] NACSELD relies on only 4 organ failures.[8] These data also show that NACSELD identifies higher-risk patients. However, the 28- and 90-day mortality risks were still substantial in patients who did not meet NACSELD: using NACSELD to define ACLF in our cohort would have missed 11,955 patients who otherwise had a high risk of death in the short term. If providers use the ACLF-NACSELD criteria to triage patients for higher level of care, the lack of ACLF-NACSELD should prompt providers to consider the CANONIC study criteria for better prediction of death (Tables S8–9 and Fig. 3).

The prevalence of ACLF in patients with decompensated cirrhosis ranges in different reports from 24% to 40%.[1,2,8] Ours is the first study to report on temporal trends in the prevalence and outcomes of ACLF. Two additional clinical findings of our work include mortality outcomes in patients with ACLF-3 over the years and mortality outcomes in transplant centres. The advancement of inpatient medical care, including the development of sepsis bundles, rapid response teams, may be the reason why some of the mortality rates associated with different grades of ACLF have reduced over the past decade; however, it is still concerning that the survival of patients ACLF-3 has not improved which could be due to lack of early recognition and intervention. Along the same lines, care of patients with cirrhosis may be different in centres with less advanced comprehensive care of critically ill patients with cirrhosis, which explains why transplant centres do better than non-transplant centres with regard to short-term mortality for both patients with and without ACLF. At the VA hospitals between 2004 and 2014, only 514 (0.03%) of patients meeting ACLF criteria were transplanted and only 45 of 2,545 meeting ACLF-3 criteria were transplanted (0.02%). Given the dismal outcomes of patients with ACLF-3, it is important that clinicians recognise this syndrome as a different entity, not as *mere decompensation* and start liver transplant evaluation, which, at the VA should trigger a referral to the National Surgery Office to improve transplant outcomes at the VA.[9–11]

In contrast to other reported large cohorts with ACLF, our study cohort was racially diverse with 19% AAs and 71% Whites. We found that AAs were more likely to have ACLF but were less likely to die at 28 and 90 days than Whites. There was a higher prevalence of ACLF-1 and ACLF-2 in AAs than in Whites, both associated with lower mortality rate than ACLF-3 (Tables S6–7). However, the survival benefit for AAs persisted in analysis stratified by ACLF stage and this may be related to intrinsic biological differences as AAs may be more resistant to infections and/or mount a better inflammatory response compared with their White counterparts.[12]

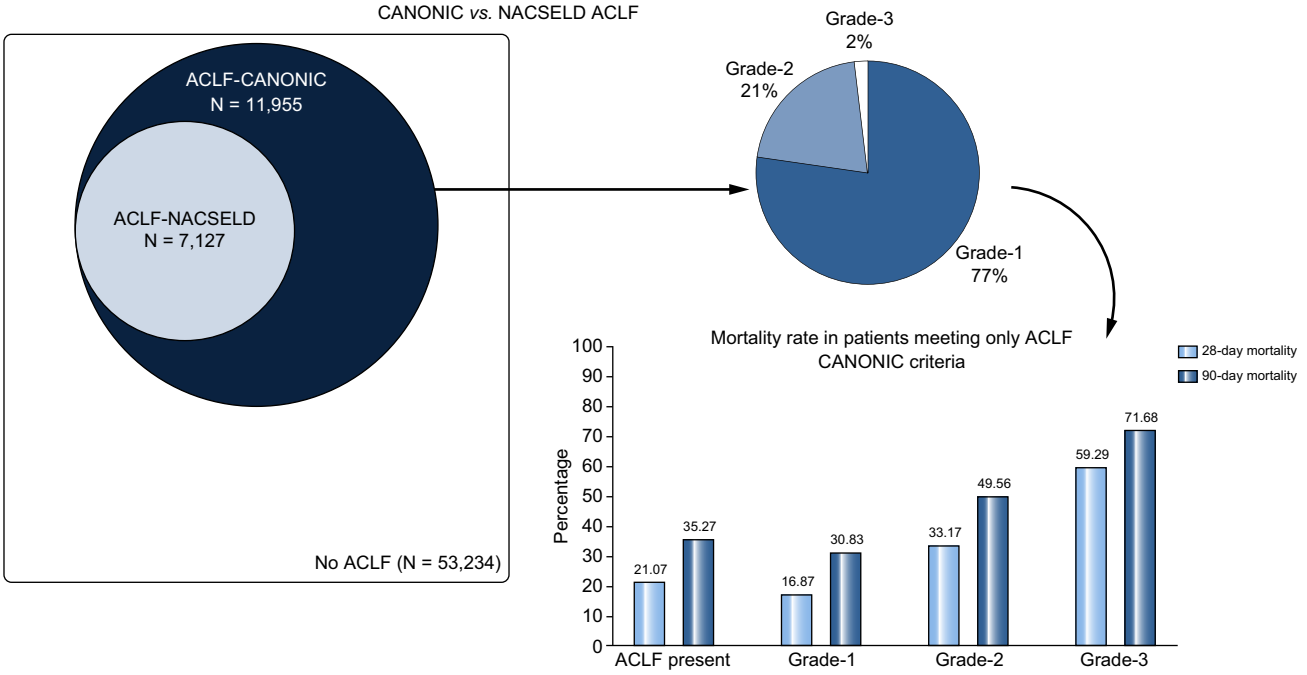



**Fig. 4. Annual ACLF prevalence and 28-day mortality for patients hospitalised with ACLF between 2004 and 2014.** First, we fitted a logistic regression model with mortality rate at 28 and 90 days as the binary outcome and time (year) as a predictor, and subsequently fitted a hierarchical generalised linear model to account for the variance in patient outcomes within time and between patients. ACLF, acute-on-chronic liver failure.

Although our study is the largest up to date on ACLF outcomes, it has several limitations. The retrospective nature of the data limited the ability to capture the exact parameters associated with some organ failures definitions such as hepatic encephalopathy (*e.g.* West Haven grade I or II), respiratory failure (*e.g.* partial pressure of oxygen in arterial gas), circulatory failure (*e.g.* exact doses of vasopressors). We believe that misclassification in our data would be differential and that more organ failures would be called as *no organ failure,* and thus, it is possible that our estimates are an underestimate. With regard to other triggers, we opted to choose alcohol use documented in the past year. Although this is not as accurate as data history taken to reflect alcohol consumption in the past 3 months,[2] we think that patients tend to underestimate alcohol use. Alcohol misuse is better captured by 1 year of either AUDIT-C values, or ICD-9 codes reflecting alcohol consumption. We also did not have detailed information to determine aetiology of cirrhosis in 36.3% of patients. However, most patients in the group (without a known aetiology) had a body mass index ≥30 kg/m$^2$ (61.2% *vs.* 47.1% in the group with HCV or alcohol, data not shown), suggesting that they might have non-alcoholic fatty liver disease as the underlying risk factor for cirrhosis. We chose ICD diagnosis for HCC as a surrogate of cirrhosis because cirrhosis itself is the strongest risk factor for the development of HCC and found no changes in the key results after removing 1,429 patients that only met cohort inclusion criterion on the basis of HCC alone (Tables S4–5 and Fig. S1). The current study population included only patients with decompensated cirrhosis admitted to any of the 127 VA facilities from 2004 to 2014, regardless of the level of care. We believe this is one of the strengths of our study: all participants were under the same healthcare model and benefits and, thus, the results were likely not affected by differential access to healthcare. We did not address the development of new ACLF in patients with mere acute decompensation. Future work will examine the risk and predictors of ACLF in patients with prior acute decompensation (but *no ACLF*) over different follow-up times and determine whether frequent decompensations lead to different ACLF phenotypes.

In summary, we found that 1 in 4 patients with decompensated cirrhosis in the VA population had ACLF, and 1 in 4 would die within 28 days and 1 in 2 within 90 days. Although the mortality risk decreased over time, it remains high. Early identification and intervention with bundles of care and referral to transplant centres are likely to improve survival outcomes in this population.

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## Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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

## Authors' contributions

JRK, RH, and FK: concept and design, data analysis, writing of article, and critical revision of the article. YL, AT, YN, KBH, PG, ES, RM, AG: data analysis and critical revision of the article. HBE-S: data analysis, writing of article, and critical revision of the article.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.018.

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