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Drug-Induced Acute-on-Chronic Liver Failure in Asian Patients

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OBJECTIVES: **Acute insults from viruses, infections, or alcohol are established causes of decompensation leading to acute-on-chronic liver failure (ACLF). Information regarding drugs as triggers of ACLF is lacking. We examined data regarding drugs producing ACLF and analyzed clinical features, laboratory characteristics, outcome, and predictors of mortality in patients with drug-induced ACLF.**

METHODS: **We identified drugs as precipitants of ACLF among prospective cohort of patients with ACLF from the Asian Pacific Association of Study of Liver (APASL) ACLF Research Consortium (AARC) database. Drugs were considered precipitants after exclusion of known causes together with a temporal association between exposure and decompensation. Outcome was defined as death from decompensation.**

RESULTS: **Of the 3,132 patients with ACLF, drugs were implicated as a cause in 329 (10.5%, mean age 47 years, 65% men) and other nondrug causes in 2,803 (89.5%) (group B). Complementary and alternative medications (71.7%) were the commonest insult, followed by combination antituberculosis therapy drugs (27.3%). Alcoholic liver disease (28.6%), cryptogenic liver disease (25.5%), and non-alcoholic steatohepatitis (NASH) (16.7%) were common causes of underlying liver diseases. Patients with drug-induced ACLF had jaundice (100%), ascites (88%), encephalopathy (46.5%), high Model for End-Stage Liver Disease (MELD) (30.2), and Child-Turcotte-Pugh score (12.1). The overall 90-day mortality was higher in drug-induced (46.5%) than in non–drug-induced ACLF (38.8%) ($P = 0.007$). The Cox regression model identified arterial lactate ($P < 0.001$) and total bilirubin ($P = 0.008$) as predictors of mortality.**

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LIVER

DISCUSSION: **Drugs are important identifiable causes of ACLF in Asia-Pacific countries, predominantly from complementary and alternative medications, followed by antituberculosis drugs. Encephalopathy, bilirubin, blood urea, lactate, and international normalized ratio (INR) predict mortality in drug-induced ACLF.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/A162

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INTRODUCTION

Patients with preexisting chronic liver disease (CLD) are uniquely susceptible to develop liver failure from acute liver injury (1,2). Acute liver injury may occur from alcohol (3,4) and viruses such as hepatitis A, B, or E (5,6). Other precipitants include drugs and toxins. Often precipitating insults cannot be identified (7). Furthermore, CLD by itself is a risk factor for developing infections such as tuberculosis (8,9), cellulitis, or spontaneous bacterial peritonitis, which can influence outcome. Indeed, some drugs such as combination antituberculosis drugs used in the setting of CLD can negatively impact outcome.

Although, typically, the presence of underlying CLD does not increase the overall susceptibility of drug-induced liver injury (DILI), with certain exceptions that are stated below, recovery from DILI is less likely, given the reduced hepatic functional reserves and capacity for adaptation (10,11). Although most drugs are safely tolerated in the setting of CLD, recent work suggests that individuals with CLD may be at an increased risk of developing hepatotoxicity at least to certain drugs (12). Often, several factors may act in concert to increase the risk of liver injury. For example, in patients with CLD or cirrhosis, CYP 450 enzymes are differentially affected (13). Furthermore, mitochondrial dysfunction, portosystemic shunting, and alteration of protein binding may modify the pharmacokinetic and pharmacodynamic characteristics of drugs (13,14), resulting in increased exposure to drug levels or their metabolites and reduced clearance. Recent work from the drug-induced liver injury network from United States has demonstrated that patients with preexisting liver disease had a higher risk of death from DILI (16%) than those without (5%) (15). Although most drugs are safe in cirrhosis, drugs that have been implicated as triggering liver injury include antituberculous drugs, methotrexate, and antiretroviral drugs in HIV/AIDS-infected individuals, particularly in the setting of underlying hepatitis B or C (10,11,14,16–18).

Moreover, the effect of drugs in patients with cirrhosis is poorly studied; such patients are commonly excluded from clinical trials (11). Furthermore, cirrhosis or CLD is highly heterogeneous in nature, with differential contribution of fibrosis, functioning liver cells, collateral formation, and extent of portal hypertension, all of which impact outcome (10).

There is growing recognition of the unique characteristics, natural history, complications, and outcome of patients who develop acute-on-chronic liver failure (ACLF) (2,19). Information from acute insults such as alcohol, infection, and organ failure has been reported. However, information regarding drugs as acute insults precipitating ACLF is lacking (20).

We aimed to study the proportion of patients with ACLF precipitated by drugs, the type of drugs, natural history, and outcome of drug-induced ACLF across a large, multicenter, internationally representative Asia-Pacific region registry on ACLF. We compared the characteristics of drug-induced with non–drug-induced ACLF. We also analyzed the predictors of mortality and compared the ability of prognostic models to predict outcome.

PATIENTS AND METHODS

Patients with ACLF secondary to drugs were identified from the ACLF Asian Pacific Association of Study of Liver (APASL) Research Consortium (AARC) database. AARC is a multinational consortium of 29 countries and 52 investigators where patient data in the age group 17–70 years with ACLF are collected prospectively in a predesigned web-based proforma (www.aclf.in). The nodal point where the data are housed and managed is the Institute of Liver and Biliary Sciences (ILBS), New Delhi. The Institute Ethical Committee, i.e., the Institutional Ethics Committee/Institutional Review Board of ILBS *vide* letter no F25/5/64/ILBS/AC2013/912, has approved the study. Informed consent was obtained from patients, and they are followed up regularly to assess outcome for up to 3 months. Patients were considered to have ACLF when they fulfilled established APASL defining criteria: "acute hepatic insult manifesting as jaundice (total bilirubin >5 mg/dL) and coagulopathy (international normalized ratio (INR) >1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed CLD (1,21).

The focus of this study was on drugs as precipitants of acute insults in the development of ACLF. Because there is no objective confirmatory laboratory test to establish a diagnosis of DILI and because patients with CLD may have elevated baseline liver chemistry, the diagnosis of drug-induced ACLF was largely based on a strong temporal relationship between exposure to drug(s) and onset of ACLF together with a rigorous exclusion of competing causes (including acute flare from hepatitis B and C) and others as stated below. Patients had to fulfill all 6 criteria as listed below.

1. DILI in patients with preexisting liver disease was defined as elevation of transaminase levels that were at least 2–3 times baseline levels or bilirubin levels more than 2 times baseline (22) but also fulfilling criteria for ACLF
2. A strong temporal relationship between exposure to the drug and recent development of ACLF defined as total bilirubin >5 mg/dL and INR >1.5 together with either ascites and/or encephalopathy.
3. Patients with increased transaminases alone (regardless of the fold increase) without the concomitant bilirubin increase of >5 mg/dL and INR >1.5 and not fulfilling clinical criteria such as ascites and/or encephalopathy were not included.
4. Competing causes such as acute viral hepatitis A and E and flares from B and C and autoimmune causes were ruled out after appropriate negative virological and serological tests.

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5. Patients with a history of decompensation such as ascites, encephalopathy, jaundice, or variceal bleed were excluded.
6. At least 1 imaging study including ultrasonography or contrast-enhanced computed tomography, which excluded biliary obstruction or biliary abnormality.
7. Liver biopsy mostly from the transjugular route was performed whenever indicated for diagnosis and better characterization of CLD.

The diagnosis of drug-induced ACLF was made by the leading physician at the contributing site. The offending drug that was considered a likely culprit was stopped immediately. We investigated the different agents/class of drugs causing ACLF, the baseline admission clinical features and laboratory characteristics and its impact on 3-month mortality. We also compared the common groups causing drug-induced ACLF.

Statistical analysis

Categorical variables were presented as proportions, whereas continuous variables were either presented as mean with s.d. or median with interquartile range. The chi-square test or Fisher exact test was used for categorical variables. Normally distributed continuous variables were compared using the Student *t* test. Non-normal continuous variables will be compared using the Mann-Whitney *U* test (unpaired data). Prognostic predictors of death at baseline, day 4, and day 7 were analyzed using Cox regression in univariate and multivariate analyses. The cumulative probability of survival was depicted using a Kaplan-Meier graph and was compared using the log-rank test. $P < 0.05$ was considered as significant. All statistical tests were performed using SPSS for Windows version 22 (Armonk IBM Corp).

RESULTS

Between April 2009 and April 2018, we analyzed 3,132 patients with ACLF with complete data including 3-month follow-up. Drugs were considered triggers of acute insults in 329 cases constituting 10.5% of cases. Men outnumbered women (64.7% vs 35.3%). Antituberculosis therapy (ATT) drugs and complementary and alternative medicines (CAMs) constituted 27.3% (n = 90) and 71.7% (n = 236), respectively, whereas the remaining 1% (n = 3) were from methotrexate (n = 2) and likely anti-epileptic drug (n = 1). The median duration of drug use in which data were available was 84 days. One hundred fifty-three patients (46.5%) died, of whom 42 (46.7%), 110 (46.4%), and 1 patient (33%) died of ATT, CAM and non-ATT-non-CAM drugs, respectively. Table 1 shows the characteristics of patients with and without drugs as acute insult including disease severity scores. Patients with drug-induced ACLF were more likely to be women (52.3%) compared with 28.5% in nondrug causes of ACLF (Table 1). Table 2 illustrates the differences between survivors and nonsurvivors in the drug group. Nonsurvivors were significantly exposed to CAM and ATT drugs and demonstrated a higher proportion of encephalopathy, including worse indexes of liver function (bilirubin and INR), serum creatinine, and Model for End-Stage Liver Disease (MELD), APASL, ACLF Research Consortium (AARC), and other severity scores.

Causes of underlying CLD

The causes of underlying liver diseases were as follows: alcohol-associated disease (28.6%; n = 94), cryptogenic liver disease (25.5%; n = 84), hepatitis B–related disease (17.3%; n = 57), nonalcoholic steatohepatitis (16.7%; n = 55), autoimmune hepatitis (5.5%; n = 10), hepatitis C virus (3.3%; n = 11), and others (3%; n = 10).

Liver biopsy was performed in 532/3,132 (17%) in the ACLF cohort. Eighty-nine of 329 cases (27.05%) of the ACLF-DILI underwent liver biopsy. Histological confirmation of cirrhosis was noted in 76/89 cases (85.39%) of ACLF from drugs including 19 patients who received anti-TB drugs.

Comparison between ATT drugs and CAMs

Because ATT drugs and CAMs constituted 99% of drugs as triggers for ACLF, we compared the characteristics between ATT drugs and CAMs, which is depicted in Table 3. Except for a female preponderance in the ATT-DILI group, others including liver biochemistry and liver disease severity scores were similar. Mortality was also similar (46%). The overall median survival time was 23.5 days from admission (range 12.6–34.7 days), which was shorter for CAMs compared with ATT drugs (22 vs 31 days).

Characteristics between survivors and nonsurvivors

The presence of encephalopathy is an indicator of poor survival. Total bilirubin, INR, serum creatinine, and lactate were significantly elevated in nonsurvivors (Table 2). All liver disease severity scores were significantly elevated in nonsurvivors. The total leukocyte count, a marker of inflammation or infection, was also highly predictive of mortality. Of note, transaminase levels were not significant. Underlying liver disease also did not contribute toward mortality. The mean body mass index between survivors (24.8 ± 4.1) and nonsurvivors (24.4 ± 4.9) was not significant ($P = 0.6$).

Multivariate analysis. Table 4 shows the dynamic model from baseline to day 7. Lactate (hazard ratio 1.6–4) was consistently a predictor of mortality from baseline to day 7, whereas bilirubin was the other indicator of mortality (hazard ratios 1 and 2.4 at baseline and 1 week, respectively).

Predictors of 90-day mortality. Predictors of mortality from baseline variables in patients with ACLF-DILI are shown in Table 5. Encephalopathy, INR, bilirubin, and lactate were significant. The area under receiver operating characteristic (AUROC) with sensitivity and specificity is shown in Figure 1.

We analyzed liver disease severity models and found the AARC Model and MELD scores are better indicators of mortality with an ROC of 0.75 and 0.74, respectively (Figure 2).

DISCUSSION

The results from a large multicenter registry showed drugs constituting 10.5% of acute insults in patients presenting with ACLF. Furthermore, overall mortality from drug-induced ACLF was 46.5%, which was significantly higher than 38.8% from nondrug causes ($P = 0.007$). However, mortality between anti-TB drugs and CAMs was similar (46%). ACLF from drugs did not have any specific characterization, except the proportion of females was 53.3% compared with 28.5% in non–drug-induced ACLF (Table 1), which is in line with studies on DILI (15,23) together with higher mortality across many DILI registries (15,23,24). Of note, our cohort included only patients with severe liver disease as any increase in aminotransferase without a concomitant increase in bilirubin levels of >5 mg/dL and INR > 1.5 were excluded.

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Table 1. Comparison of the baseline parameters among ACLF cases with acute insult from drugs vs others

Variable	ACLF (drugs) Group A n = 329	ACLF (nondrugs) Group B n = 2,803	*P* value
Age (yr)	46.9 ± 13.72	44.23 ± 12.07	0.001
Sex, male	213 (64.7%)	2,446 (87.5%)	<0.001
Etiology of acute insult (n, %)			
Antituberculosis drugs	90 (27.4)		
Complementary, Ayurvedic, and HDS	187 (56.8)		
Non-ATT, non-CAM, non-HDS	52 (15.8)		
Etiology of chronic disease (n, %)			
Alcoholic disease	92 (28)	1,454 (56.6)	<0.001
Cryptogenic disease	236 (72)	1,115 (43.4)	<0.001
Clinical presentation (n, %)			
Jaundice	329 (100)	2,803 (100)	NA
Ascites	289 (88.4)	2,263 (88.5)	0.779
Encephalopathy	145 (46.5)	1,094 (45.1)	0.672
Laboratory parameters			
Hemoglobin (g/dL)	10.91 ± 2.34	10.52 ± 2.26	0.002
WBC (10^3/dL)	10.7 (1.6–44.3)	11.3 (1–201)	0.045
Platelets (10^3/dL)	126 (10–495)	129 (2.16–803)	0.558
PT-INR	2.29 (1.5–11.14)	2.13 (1.5–25.3)	<0.001
Total bilirubin (mg/dL)	21.54 ± 8.99	19.94 ± 9.74	0.002
Direct bilirubin (mg/dL)	12.87 ± 6.18	12.42 ± 6.56	0.223
AST (IU/L)	163 (16.8–6,980)	147 (2.5–7,552)	0.019
ALT (IU/L)	86 (1.28–2,770)	60 (0.08–4,986)	<0.001
ALP (IU/L)	125 (27–1,132)	119 (4–1,590)	0.246
GGT (IU/L)	53 (9–634)	76 (1.8–1,536)	<0.001
Albumin (g/dL)	2.26 ± 0.61	2.37 ± 0.65	0.004
Urea (mg/dL)	31 (1.9–352.1)	31.62 (0.2–343)	0.680
Serum creatinine (mg/dL)	0.87 (0.01–9.22)	1 (0–15.28)	0.003
Serum Na (meq/l)	131.68 ± 7.6	131.2 ± 7.6	0.32
Lactate (mg/dL)	2 (0.1–22)	1.9 (0.1–44.1)	0.395
Disease severity score			
CTP	12.01 ± 1.49	11.96 ± 1.44	0.373
MELD score	30.22 ± 7.17	28.86 ± 7.08	<0.001
APACHE score	15.63 ± 6.16	16.49 ± 6.89	0.154
CLIF-SOFA	11.62 ± 2.55	11.51 ± 2.75	0.445
AARC score	10.19 ± 2.2	10.01 ± 2.1	0.25
SOFA	9.23 ± 3.35	9.02 ± 3.12	0.276
Mortality at 90 d (n, %)	153 (46.5)	1,088 (38.8)	0.007

AARC, APASL ACLF Research Consortium; ACLF, acute-on-chronic liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; ATT, antituberculosis therapy; CAM, complementary and alternative medication; CLIF-SOFA, Chronic Liver Failure- Sequential Organ Failure Assessment; CTP: Child-Turcotte-Pugh; GGT, Gamma glutamyl transferase; HDS, herbal and dietary supplement; HE, hepatic encephalopathy; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; SOFA, Sequential Organ Failure Assessment; ST, aspartate aminotransferase; TLC, total leucocyte count; WBC, white blood count.

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Table 2. Baseline characteristics between survivors and nonsurvivors in the ACLF-DILI cohort

Variable	Survivors n = 176 (53.5)	Nonsurvivors n = 153 (46.5)	*P* value
Age (yr)	45.52 ± 13.51	48.58 ± 13.83	0.065
Sex, male	118 (67%)	95 (62.1%)	0.357
Etiology of acute insult (n, %)			**0.002**
Antituberculous drugs	48 (27.3)	42 (27.5)	
Complementary, Ayurveda, and HDS	89 (50.6)	98 (64.1)	
Non-ATT, non-CAM, non-HDS	39 (22.2)	13 (8.5)	
Etiology of chronic disease (n, %)			**0.269**
Alcoholic disease	54 (30.7)	38 (25)	
Cryptogenic disease	122 (69.3)	114 (75)	
Clinical presentation (n, %)			
Jaundice	176 (100)	153 (100)	NA
Ascites	137 (90.1)	152 (86.9)	0.390
Encephalopathy	60 (36.6)	85 (57.4)	<0.001
Laboratory parameters			
Hemoglobin (g/dL)	11.03 ± 2.23	10.78 ± 2.47	0.299
WBC (10^3/dL)	9.65 (1.6–44.3)	11.6 (3.65–41.5)	0.004
Platelets (10^3/dL)	130 (15–495)	122.5 (10–474)	0.65
INR	2.39 ± 0.98	3.18 ± 1.55	<0.00
Total bilirubin (mg/dL)	19.50 ± 8.61	23.87 ± 8.87	<0.001
Direct bilirubin (mg/dL)	12.0 ± 5.88	13.88 ± 6.38	0.20
AST (IU/L)	159 (21–2,947)	173 (16.8–6,980)	0.171
ALT (IU/L)	85 (1.29–2,307)	89 (1.55–2,770)	0.732
ALP (IU/L)	130 (27–1,132)	112 (30–781)	0.049
GGT (IU/L)	54.5 (9–439)	49 (10–634)	0.503
Albumin (g/dL)	2.26 ± 0.62	2.27 ± 0.59	0.613
Urea (mg/dL)	27.74 (2.7–296)	35 (1.9–352.1)	0.008
Serum creatinine (mg/dL)	0.8 (0.01–9.22)	1.03 (0.15–8.87)	0.003
Serum Na (meq/L)	131.7 ± 7.8	131.6 ± 7.5	0.96
Lactate (mg/dL)	1.9 (0.6–22)	2.1 (0.1–21.9)	0.020
Disease severity score			
CTP	11.75 ± 1.32	12.30 ± 1.62	0.020
MELD score	27.51 ± 6.40	33.29 ± 6.76	<0.001
APACHE score	14.33 ± 5.27	16.76 ± 6.65	0.038
AARC score	10.98 ± 1.88	9.27 ± 2.08	<0.001
CLIF-SOFA	10.91 ± 2.31	12.26 ± 2.59	<0.001
SOFA	8.33 ± 2.61	10.12 ± 3.76	<0.001

AARC, APASL ACLF Research Consortium; ACLF, acute-on-chronic liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; ATT, antituberculosis therapy; CAM, complementary and alternative medication; CLIF-SOFA, Chronic Liver Failure- Sequential Organ Failure Assessment; CTP: Child-Turcotte-Pugh; GGT, Gamma glutamyl transferase; HDS, herbal and dietary supplement; HE, hepatic encephalopathy; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; SOFA, Sequential Organ Failure Assessment; ST, aspartate aminotransferase; TLC, total leucocyte count; WBC, white blood count.

It is commonly believed that patients with cirrhosis are not at a higher risk of DILI (10), but complications from DILI may result in a less favorable outcome because of diminished hepatic functional reserves and decreased ability to mount an adaptive response. The high mortality of 46.6% is indicative of this fact and is supported by the 16.5% mortality in individuals with preexisting liver disease from the DILIN series compared with 5% in those without CLD, highlighting the real and subtle

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Table 3. Comparison between ACLF-DILI cases due to ATT drugs and CAMs

Variable	ATT drugs N = 90	CAMs N = 236	*P* value
Age (yr)	46.9 ± 14.1	46.9 ± 13.6	1.0
Sex, male	42 (46.7%)	170 (72.0%)	<0.001
Clinical presentation (n, %)			
Jaundice	90 (100%)	236 (100%)	
Ascites	79 (88.8%)	194 (87.4%)	0.74
Encephalopathy	44 (50.0%)	101 (45.7%)	0.49
Laboratory parameters			
Hemoglobin (g/dL)	10.5 ± 2.05	11.05 ± 2.4	0.06
WBC (10^3/dL)	9.6 (1.6,35.2)	11.14 (2.4,44.3)	0.02
Platelets (10^3/dL)	122 (10,449)	26 (15,495)	0.22
INR	2.3 (1.5,11.14)	2.24 (1.5,7.7)	0.81
Total bilirubin (mg/dL)	20.5 ± 8.6	21.9 ± 9.1	0.18
Direct bilirubin (mg/dL)	12.0 ± 5.7	13.2 ± 6.4	0.11
AST (IU/L)	136.5 (37,2947)	170 (16.8,6980)	0.12
ALT (IU/L)	76.5 (16,2419)	91 (1.29,2770)	0.55
ALP (IU/L)	132 (27,781)	121 (39,1132)	0.32
GGT (IU/L)	26.75 (2.7,296)	34 (1.9,352.1)	0.30
Albumin (g/dL)	2.29 ± 0.62	2.26 ± 0.61	0.71
Urea (mg/dL)	26.75 (2.7,296)	34 (1.9,352.1)	0.006
Serum creatinine (mg/dL)	0.81 (0.15,9.2)	0.91 (0.01,7.4)	0.11
Serum Na (meq/L)	132.5 ± 8.30	131.4 ± 7.4	0.26
Lactate (mg/dL)	2.3 (1.0,21.9)	1.9 (0.1,22)	0.02
Disease severity score			
CTP	12.0 ± 1.57	12.02 ± 1.47	0.70
MELD score	29.9 ± 7.18	30.38 ± 7.21	0.61
APACHE score	14.6 ± 5.8	16.1 ± 6.30	0.17
CLIF-SOFA	11.6 ± 2.26	11.6 ± 2.67	0.95
AARC score	10.21 ± 2.14	10.2 ± 2.16	0.81
SOFA	9.0 ± 3.6	9.4 ± 3.3	0.52
90-d mortality (n, %)	42 (46.7%)	110 (46.6%)	0.99

AARC, APASL ACLF Research Consortium; ACLF, acute-on-chronic liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; ATT, antituberculosis therapy; CAM, complementary and alternative medication; CLIF-SOFA, Chronic Liver Failure- Sequential Organ Failure Assessment; CTP: Child-Turcotte-Pugh; GGT, Gamma glutamyl transferase; HDS, herbal and dietary supplement; HE, hepatic encephalopathy; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; SOFA, Sequential Organ Failure Assessment; ST, aspartate aminotransferase; TLC, total leucocyte count; WBC, white blood count.

Table 4. Factors influencing mortality dynamically in drug-induced cases by multivariate Cox regression analysis

	Baseline		Day 4		Day 7	
Parameter	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Urea	1.373 (1.097,1.716)	0.006	1.378 (1.044, 1.818)	0.024		
Lactate	1.678 (1.203,2.342)	0.002	4.419 (3.047, 6.407)	<0.001	4.035 (2.715, 5.997)	<0.001
INR	4.028 (2.401,6.759)	<0.001				
HE	1.566 (1.051,2.333)	0.027				
Total bilirubin	1.035 (1.012,1.058)	0.002			2.441 (1.265, 4.711)	0.008

CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio; INR: International Normalized Ratio.

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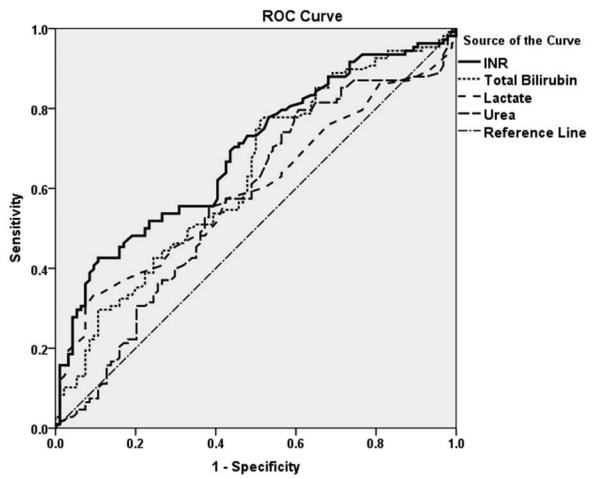
Table 5. Predictor of 90-d mortality in patients with ACLF-DILI from baseline variables

	Univariate			Multivariate		
Parameter	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.014	1.002, 1.026	0.022			
TLC	1.606	1.205, 2.141	0.001			
INR	4.286	2.966, 6,193	<0.001	4.028	2.401, 6.759	<0.001
Urea	1.370	1.135, 1,655	0.001	1.373	1.097, 1.716	0.006
Creatinine	1.505	1.249, 1.813	<0.001			
Total bilirubin	1.039	1.02, 1.057	<0.001	1.035	1.012, 1.058	0.002
Lactate	2.065	1.515, 2.815	<0.001	1.678	1.203, 2.342	0.002
HE	2.335	1.68, 3.24	<0.001	1.566	1.051, 2.333	0.027

ACLF, acute-on-chronic liver failure; CI, confidence interval; DILI, drug-induced liver injury; HE, hepatic encephalopathy; HR, hazard ratio; INR, International Normalized Ratio; TLC, total leucocyte count.

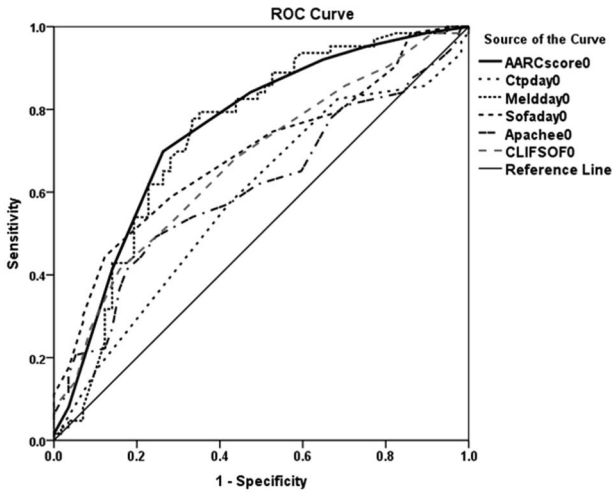
risks of liver injury and mortality in such patients (15). Traditional markers of liver injury such as elevated AST and ALT may not be reliable signals in individuals with preexisting liver disease (24). Others such as elevated bilirubin and coagulopathy may be more appropriate and indicative of severe liver injury (24). This is reflected in our series in which transaminase elevation was only 2- to 4-fold, whereas there was a marked increase in bilirubin and INR. The mild elevation of transaminase, but marked elevation of bilirubin, has been reported before and may be a feature specific to ATT drugs or CAMs (25). Indeed, even in patients without preexisting liver disease, the modest increase in transaminase in relation to bilirubin has been described in antituberculosis therapy DILI (26).

Patients with cirrhosis are a heterogeneous group with variable levels of fibrosis, inflammation, and portal hypertension, all of which play a differential role in the metabolism of drugs. Patients with cirrhosis have altered pharmacokinetic and pharmacodynamic profile (10). Although there are no specific guidelines for administering drugs in patients with preexisting liver disease, guidelines for antituberculous drugs from different societies have been in place; these are often not clear and are variably followed (27). The commonest underlying liver disease was alcohol-associated liver disease. That a quarter of patients in our series had cryptogenic liver disease is not surprising, given the increasing incidence of obesity and diabetes mellitus in the population. Because our online data do not capture information on the presence or absence of diabetes, we are unable to provide this information. Studies have shown that perturbations in metabolism in fatty liver cells increase the



Parameter	Area	cutoff	P value	sensitivity	specificity
INR	0.69	2.35	<0.001	60.2	60.4
T. Bilirubin	0.64	22.45	0.001	56.5	54.3
Lactate	0.6	1.95	0.02	57.4	57.0
Urea	0.57	32.6	0.07	57.4	56.4

Figure 1. AUROC of the multivariate Cox regression model.



Parameter	Area	cutoff	P value	sensitivity	specificity
AARC	0.75	10.5	<0.001	69.8	74.00
MELD	0.74	30.0	<0.001	69.8	67.0
SOFA	0.69	9.5	<0.001	58.7	72.0
CLIF	0.67	11.5	0.001	68.3	57.0
Apachee	0.61	16.5	0.035	54.0	58.0
CTP	0.58	12.5	0.114	57.0	58.0

Figure 2. AUROC of all severity scores.

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risk of liver injury as exemplified by obesity being a risk factor for liver injury (14,16,28). Body mass index was 24.4 ± 4.8 in survivors compared with 24.8 ± 4.2 in nonsurvivors and was not significant ($P = 0.63$) in our series. Patients with CLD taking combination ATT drugs may be particularly at risk, given the large dose of each of the antituberculosis drugs together with lipophilicity of these drugs (29). Furthermore, 6 Asian countries constitute more than 60% of the world's TB population, with India itself contributing to nearly a fourth (World Health Organization report 2017).

The fact that complementary and alternative drugs rank first is also not surprising. The use of CAMs including herbal and dietary substances is ubiquitous and growing, and many of these compounds often contain multiple ingredients that are detrimental to the liver (30,31). Traditional medicines are used for all kinds of diseases in many Eastern countries and if often integrated into the health care of countries such as China, South Korea, Singapore, and India. More than 80% of the population in these countries is exposed to complementary medicines. Causality assessment is challenging in such instances, particularly when patients are exposed to multi-ingredient products, which is very common in traditional medicines including the AYUSH group of drugs. Lax regulation in production of these compounds and questionable safety and efficacy records places patients with cirrhosis at an increased risk of developing liver injury that leads to decompensation. The high mortality in patients with chronic disease from the DILIN series is in line with our results and attests to the caution that needs to be exercised in such patients (30).

There are limitations to our study. We selected only patients who fulfilled criteria for ACLF, which include bilirubin levels of >5 mg/dL and INR >1.5. Thus, we included only patients with relatively severe disease (ACLF) because those with only elevation of aminotransferase regardless of the fold increase and/or bilirubin levels <5 mg/dL were excluded. Furthermore, those without concomitant coagulopathy, ascites, or encephalopathy were excluded. A further limitation is the challenge of causality assessment in patients with preexisting liver disease, which has been highlighted in a recent review (22). Liver chemistry monitoring may be difficult to interpret in the presence of underlying CLD, especially when baseline tests are altered. Care was taken to exclude competing causes by local principal investigators. Expert opinion for causality assessment has been undertaken before, particularly in large population-based studies (32,33). We are also aware about the heterogeneity of care among the large number of contributing centers from different countries, with many lacking liver transplantation facility. Ironically, in such centers, the natural history of the disease could be observed. Attribution of antituberculosis drugs and complementary drugs as precipitants of ACLF was straightforward. However, identifying the individual constituents of CAMs was not possible. CAM, which includes traditional medicines including AYUSH (Ayurveda, Unani, Siddha, and Homeopathy), very often consists of undeclared constituents in the form of powders, pastes, and tablets (See Figure 1, Supplemental Digital Content, http://links.lww.com/AJG/A162) Very often, a single tablet consists of a number of ingredients in 1 instance up to 49. Furthermore, our online case record does not have provision to capture individual drug or component details. An example of multi-ingredient sample is shown in Supplemental Digital Content, Figure 1, http://links.lww.com/AJG/A162. Our study highlights the challenges faced with regard to causality assessment in patients with preexisting liver disease and the effort that is needed to find alternatives to RUCAM (Roussell Uclaf Causality Assessment Method). Many of the domains in RUCAM including the increase in transaminase may not be pertinent to patients with cirrhosis; patients with cirrhosis often do not mount a massive increase in transaminase; instead, increased bilirubin and/or coagulopathy may be an initial sign of injury as acknowledged in previous reports (24,30). This can be complemented with other synthetic markers such as albumin and INR. The role of cytokine profiles, microRNA-122 and HMGB-1, when these become available offers hope but needs to be validated (34), and tests of quantitative liver function that can detect functional impairment and help identify high-risk groups for decompensation are urgently needed (35).

In conclusion, CAMs and anti-TB medications constitute about a tenth of all causes of ACLF with a substantial mortality in nearly half of patients with drug-induced ACLF. Alcoholic liver disease, cryptogenic liver disease, and non-alcoholic steatohepatitis (NASH) constitute a majority of common causes of underlying liver disease. Bilirubin, INR, lactate and encephalopathy or AARC or MELD scores are more reliable signals of mortality in a setting of CLD.

CONFLICTS OF INTEREST

Guarantor of the article: Shiv K. Sarin, DM.

Specific author contributions: S.K.S. and H.D. made the study concept and design. All the AARC working party members performed the acquisition of data. A.C., P.J., and P.B. performed compilation and critical revision of data at the AARC Nodal Centre. P.J. performed statistical analysis. H.D. performed drafting of the manuscript. S.K.S. performed critical revision of the manuscript for intellectual content. S.K.S. facilitated administrative and technical support. All the coauthors approved the final draft.

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Study Highlights

WHAT IS KNOWN

- ✓ Drug-induced liver injury (DILI) causing ACLF is rare, and the proportion of ACLF secondary to DILI is unknown.
- ✓ Patients with CLD take complimentary and alternative medicine assuming it to be safe and healthy and without side effects.
- ✓ Mortality from ACLF is high.

WHAT IS NEW HERE

- ✓ Drug-induced ACLF constitutes more than 10% of causes of ACLF in the Asia-Pacific region.
- ✓ CAMs followed by antituberculosis drugs are the top 2 commonest causes of drug-induced ACLF.
- ✓ Mortality from drug-induced ACLF is high (46.6%) compared with nondrug causes (38.8%) of ACLF.

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